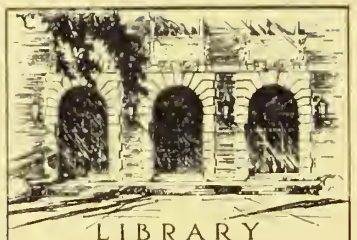


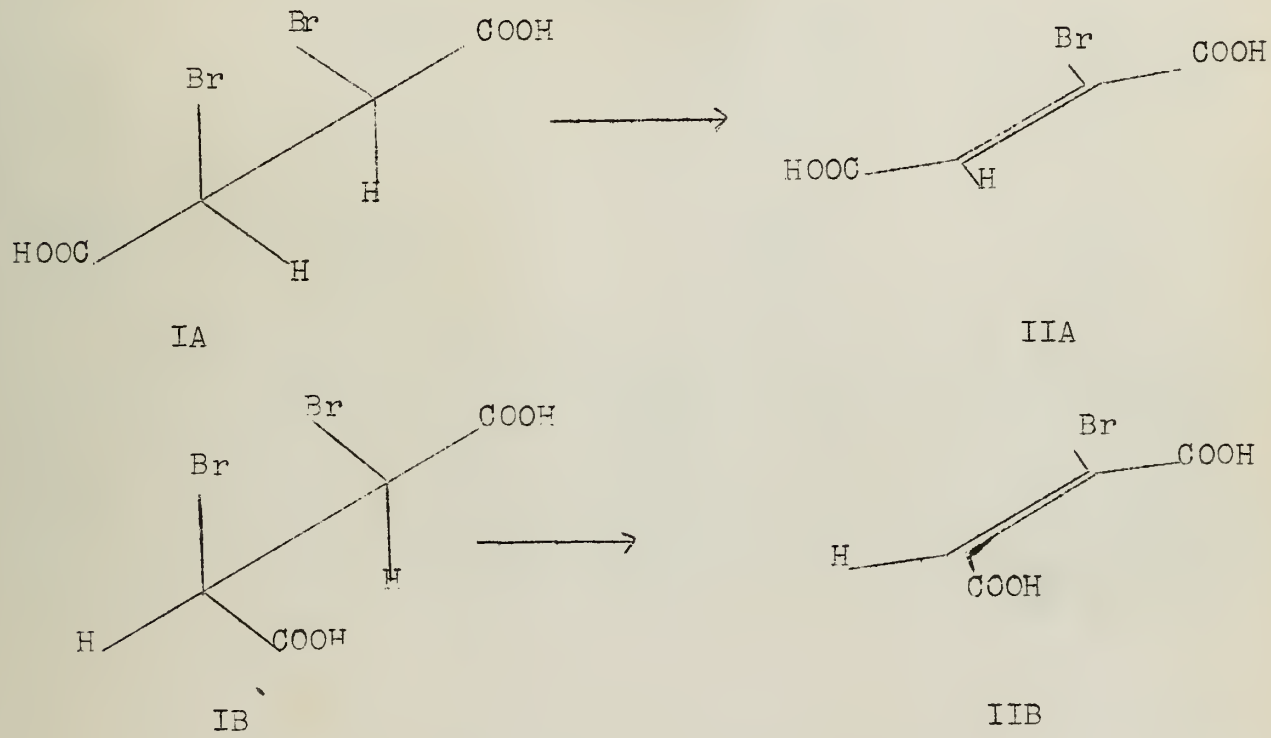
SEMINAR TOPICS

CHEMISTRY 435 I SEMESTER 1952-53

SOME RECENT DEVELOPMENTS IN THE FIELD OF ELIMINATION REACTIONS

Reported by E. J. Corey September 26, 1952

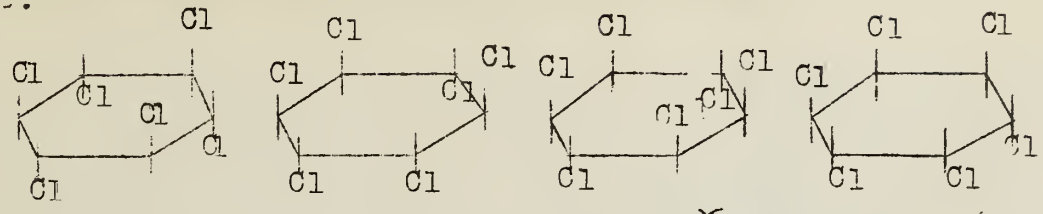
Duality of Mechanism for E2 Processes.--The stereochemistry of the olefins produced by E2 elimination reactions, e.g. base catalyzed dehydrohalogenation, for many years has been interpreted on the basis of preferential trans elimination.[1,2] Thus, while d,l-α,α'-dibromosuccinic acid (IA) upon treatment with base yields bromofumaric acid (IIA), meso-α,α'-dibromosuccinic acid (IB) affords bromomaleic acid (IIB).[3] There are numerous other examples in which trans elimination is heavily favored over cis elimination.[4-8]



Much of the recent work in the field of elimination reaction has been undertaken in order to determine (a) the circumstances under which cis elimination can occur, (b) the reasons for the relative ease with which trans elimination usually takes place and (c) whether cis and trans eliminations proceed by different mechanisms.

Cristol and his coworkers have studied the kinetics of the dehydrohalogenation of the five known isomers of benzene hexachloride, α, β, γ, δ and ε.[9-11] In the case of the α, β, γ and ε isomers the rate-determining step in the formation of trichlorobenzenes is the elimination of the first hydrogen and chlorine and, consequently the kinetics of dehydrochlorination of these substances provide information concerning the first elimination only. The β-isomer (IIIβ), which initially can undergo only cis elimination, reacts with hydroxide ion at a rate which is 7000 to 24,000 times slower than the rate of reaction of the α, γ and ε isomers (III α, γ, ε)

in which initial trans elimination is possible.



IIIβ IIIα IIIγ IIIε

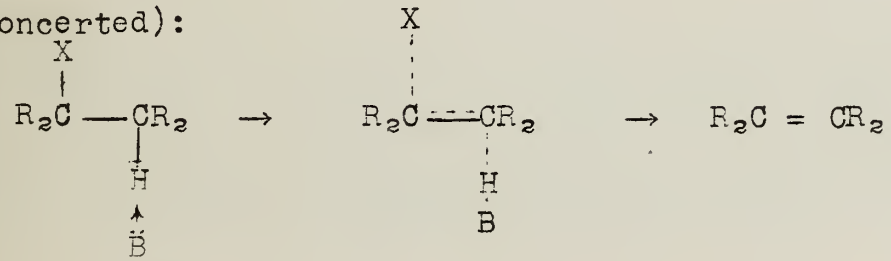
The second-order rate constants, experimental (Arrhenius) activation energies and entropies of activation for the alkaline dehydrochlorination of III β,α,γ and ε are listed in Table I.

Table I[11]

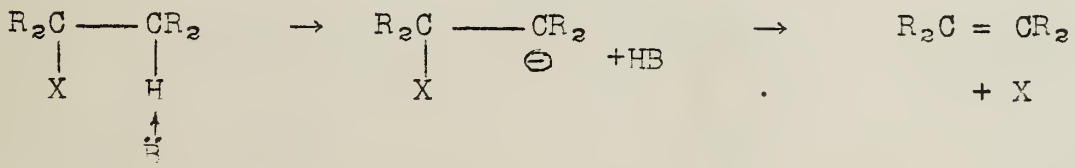
Isomer	k30.00°, l./mole sec.	ΔE_{exp}, kcal./mole	$\Delta S^{\ddagger}$, cal./mole deg.
III β	2.11.(10)$^{-5}$	31.0	20.2
III α	0.500	18.5	-1.0
III γ	0.151	20.6	3.6
III ε	0.182	21.4	6.5

It has been suggested that the large difference between the activation energies for cis and trans elimination might be due to a difference in mechanism.[9,11] As a working hypothesis it has been postulated that trans elimination proceeds by a concerted process of rather stringent steric requirements and low activation energy (A)[9,11,12] and that cis elimination cannot be concerted and proceeds via a carbanion intermediate by a two stage mechanism of relatively high activation energy and low steric requirement (B).[9,11]

A (concerted):



B (two stage):



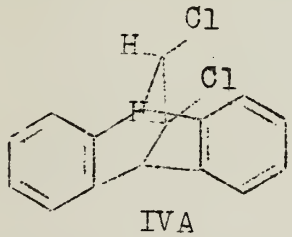
Rough calculations by Cristol[11] (which neglect the effect of solvent) indicate that the activation energy for the concerted

process should be considerably less (~7-14 kcal./mole) than that for the two-stage process.

At the present time plausible, but not compelling theoretical reasons have been adduced to explain why concerted cis elimination, if it occurs at all, should be so much slower than concerted trans elimination.[9,12] Contrary to earlier belief[5] electrostatic repulsion between the nucleophilic reagent and the departing anion, while larger for cis than for trans elimination, has been shown to be an insignificant consideration in dehydrohalogenation reactions.[11] It should be emphasized that at present there is no rigorous theoretical evidence to indicate that concerted cis elimination is not possible.

In order to determine experimentally whether cis elimination actually proceeds via a carbanion intermediate, the reaction of IIIβ with base in deuteroethanol (C_2H_5OD) was studied.[13] Introduction of deuterium into undehydrochlorinated III β during the course of reaction would be an indication of a carbanion intermediate capable of removing a deuteron from the solvent. The IIIβ recovered after one half-life of elimination contained only a small amount of deuterium and, hence, the existence of a carbanion intermediate was not demonstrated (though also not disproved) by this experiment.

The stringent steric requirements for facile trans elimination have been demonstrated quite clearly by data for the dehydrochlorination of cis - and trans - 11,12-dichloro-9,10-dihydro-9,10-ethanoanthracene (IVA and IVB).[14] Here the cis



IVA

isomer (IVA), which can undergo trans elimination, reacts about seven times more slowly than the trans isomer (IVB), which can only undergo cis elimination. Although the difference in rate is due mainly to a favorable entropy of activation for the cis process (Table II), the energy of activation for the trans process is, none the less, considerably higher than usual.

Table II

Isomer	$10^5 k110°$, l./mole sec.	ΔE_{exp}, kcal./mole	$\Delta S^{\ddagger}$, cal./mole deg.
IVA (cis)	6.38	26.5	-11.2
IVB (trans)	49.9	30.6	3.2

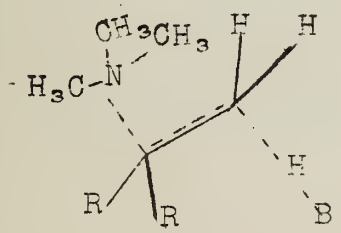
The abnormally high energy of activation for trans elimination in IVA supports the hypothesis[12,15] that the atoms involved in bond making and bond breaking must be coplanar for facile trans elimination, since the requisite coplanarity of C_{11}, C_{12} and vicinal hydrogen and chlorine is absent from IVA. Additional evidence has been brought to bear on this point by Barton and Miller in their study of the iodine-catalyzed debromination of the cholesteryl 5,6-dibromides.[15]

Comparison of the energies of activation for cis elimination in IIIβ and IVB indicates that cis elimination does not demand a very specific spatial arrangement of the atoms involved in bond making and bond breaking. This finding lends some support to the two-stage mechanism for cis elimination.

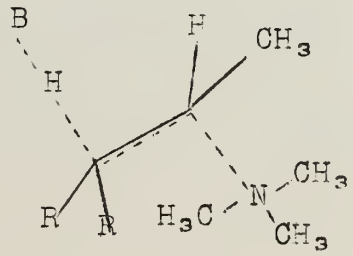
Recently Noyes and Miller[16] have studied the kinetics of dehydrohalogenation of the cis- and trans-dihaloethylenes. In each case the cis isomer (trans elimination) reacts more rapidly than the trans isomer (cis elimination). It was found, however, that the superiority of the trans process is sometimes due to a more favorable energy of activation (viz. with the dibromo-and diiodoethylenes) and sometimes due to a more favorable entropy of activation (e.g. with the dichloroethylenes).

Steric Effect in Elimination Reactions.--Hughes, Ingold et al.[12] have stated that all E1 reactions and E2 reactions with uncharged structures (e.g. halides) lead to the olefin with the most highly substituted ethylenic linkage (Saytzeff rule) and they have attributed this result to a greater degree of stabilization by hyperconjugative resonance of the transition state leading to the Saytzeff product. E2 reactions of ammonium and sulfonium salts, on the other hand, lead to the olefin with the least substituted ethylenic linkage (Hoffman rule) and it was proposed[12] that the direction of elimination in these cases is controlled by the (reaction retarding) inductive effect of the β-alkyl groups.

C. H. Schram[17] and, more recently, H. C. Brown and I. Maritani[18] have proposed that steric effects alone account for the occurrence of Hoffman elimination and that in the absence of appreciable steric effect E2 reactions always proceed according to the Saytzeff rule. The basis for this argument is that if the group being eliminated is large, e.g. $(CH_3)_3N^+$ or $(CH_3)_2S^+$, the transition state leading to the Hoffman product VA is much less strained than that leading to the Saytzeff product VB.

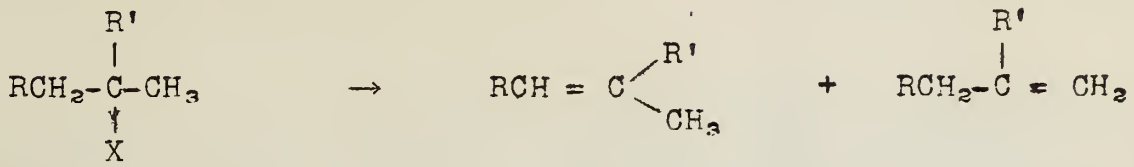


VA



VB

Table III summarizes some of the findings of Brown and Maritani for reactions of the type:



R' = alkyl or H

Table III

Reaction type	Group	Effect of increase in steric requirements of group
E1	R	Saytzeff → Hoffman
E1	X	No effect
E2	R	Saytzeff → Hoffman
E2	X	Saytzeff → Hoffman

Bibliography

1. A. Michael, J. prakt. Chem., 52, 289 (1895).
2. P. F. Frankland, J. Chem. Soc., 654 (1912).
3. R. Fittig and C. Petri, Ann., 195, 56 (1879).
4. J. Wislicenus, ibid., 248, 281 (1888).
5. W. Huckel, W. Tappe and G. Legutke, ibid., 543, 191 (1940).
6. M. C. Hoff, K. W. Greenlee and C. E. Boord, J. Am. Chem. Soc., 73, 3329 (1951).
7. D. J. Cram, ibid., 74, 2149 (1952).
8. D. Y. Curtin and D. B. Kellom, Abstracts, 122nd Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1952, p. 23M.
9. S. J. Cristol, J. Am. Chem. Soc., 69, 338 (1947).
10. S. J. Cristol, ibid., 71, 1894 (1949).
11. S. J. Cristol, N. L. House and J. S. Meek, ibid., 73, 674 (1951).
12. M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. I. Wolf, J. Chem. Soc., 2093 (1948).
13. S. J. Cristol, unpublished results.
14. S. J. Cristol and N. L. House, J. Am. Chem. Soc., 74, 2193 (1952).
15. D. H. R. Barton and E. Miller, ibid., 72, 1066 (1950).
16. S. I. Miller and R. M. Noyes, ibid., 74, 629 (1952).
17. C. H. Schram, Science, 112, 367 (1950).
18. H. C. Brown and I. Maritani, Abstracts, 122nd Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1952, p. 2M.

THE MEERWEIN REACTION

Reported by E. C. Taylor, Jr. September 26, 1952

General: In 1939, Meerwein (1) reported that, under special conditions, aromatic diazonium halides will couple with unsaturated carbonyl compounds with evolution of nitrogen to form a new carbon carbon bond. The reaction has since been extended to include the reaction of an aromatic diazonium halide with conjugated olefins, styrenes and acetylenes, with accompanying loss of nitrogen, and is known as the Meerwein reaction. The product of the reaction may be saturated or unsaturated, depending on whether the elements of HX have been lost from the initial reaction product.

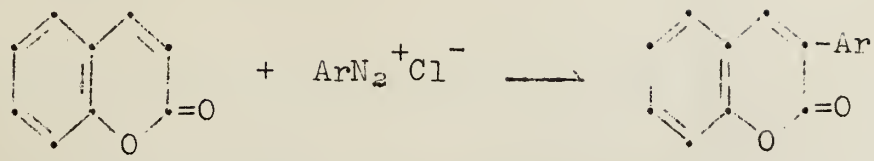
$$ArN_2^+X^- + R\text{-}CH{=}CHR' \xrightarrow{-N_2} Ar\text{-}\underset{R}{CH}\text{-}\underset{R'}{CH}\text{-}X \longrightarrow ArC{=}\underset{R}{C}\underset{R'}{H} + HX$$

Conditions: A cold solution of the diazonium halide (usually chloride) is added to a solution of the unsaturated compound in aqueous acetone containing the salt of a weak acid (usually sodium acetate) and cupric chloride. Although some cases have been found where the presence of acetone has a deleterious effect on the yield. (15,16), most workers have found that acetone is essential for the reaction. The role of the sodium acetate and cupric chloride is not clearly understood (see the section under Mechanism), although in most instances the presence of both is essential. The temperature must generally be raised to about 20° before evolution of nitrogen begins.

Scope and Limitations: The yields from the Meerwein reaction are usually low (5 - 80%) and the products are sometimes difficult to purify because of the simultaneous formation of tars, azo resins, Sandmeyer reaction products, chloroacetone and aromatic hydrocarbons. Ring substituents in the aromatic diazonium halide influence the yield greatly; for the same substituent in the o, m, and p positions, the yield of coupled product increases in the order o < m < p. In many instances, no product at all is obtained with o-substituted diazonium halides. β-Naphthalene diazonium chlorides give better yields of coupled product than α-naphthalene diazonium chlorides, probably because of a steric effect. Negative substitution ($-NO_2$, $-SO_3Na$, -Hal, -COOH, - COOR) generally leads to higher yields. The failure of positively substituted phenyl diazonium chlorides to undergo the Meerwein reaction in some instances has been reported (2,15).

Synthetic Applications: The Meerwein Reaction has been used for the preparation of the following types of compounds.

1. Aryl-substituted coumarins

(1) 

2. Cinnamic acids

(15) $ArN_2^+Cl^- + HOOC\text{-}CH{=}CH\text{-}COOH \longrightarrow Ar\text{-}CH{=}CH\text{-}COOH + CO_2 + N_2 + HCl$

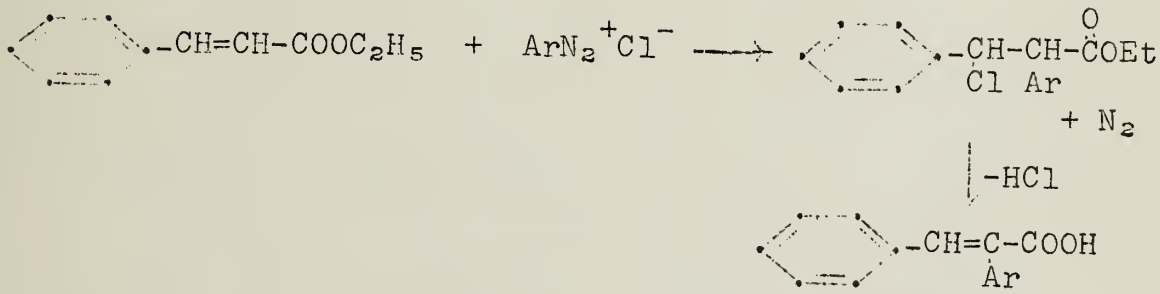
(16) $ArN_2^+Cl^- + CH_2{=}CH\text{-}COOH \longrightarrow Ar\text{-}CH{=}CH\text{-}COOH + N_2 + HCl$

(18,23,24) $ArN_2^+Cl^- + CH_2{=}CH\text{-}X \longrightarrow Ar\text{-}CH_2\text{-}\underset{Cl}{CH}\text{-}X + N_2$
$(X = -CN, -COOC_2H_5)$

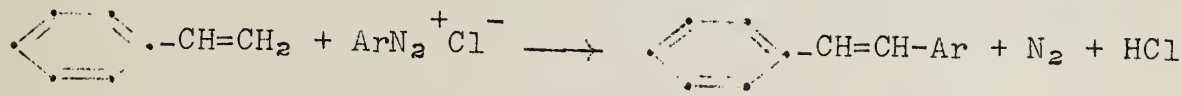
hydrolysis $\downarrow -HCl$

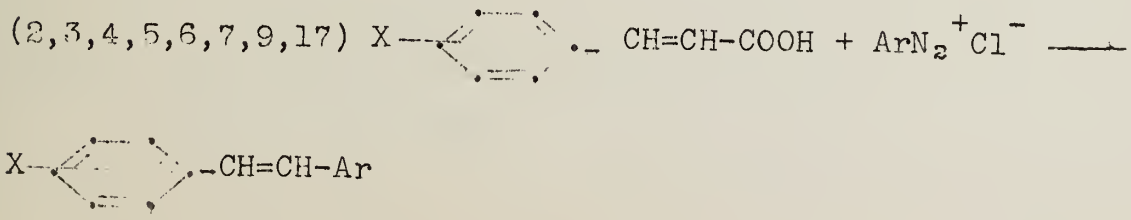
$Ar\text{-}CH{=}CH\text{-}COOH$

a. α-Aryl cinnamic acids

(1) 

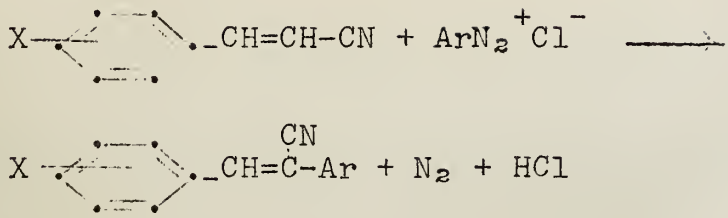
3. Stilbenes

(13) 

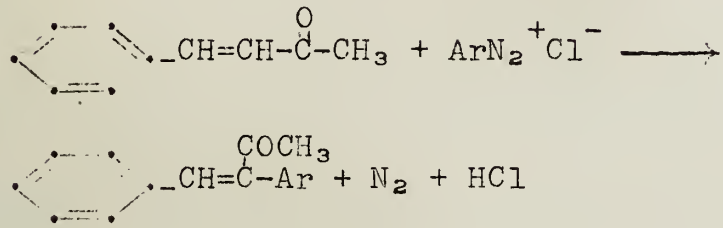
(2,3,4,5,6,7,9,17) 

$+CO_2 + HCl + N_2$

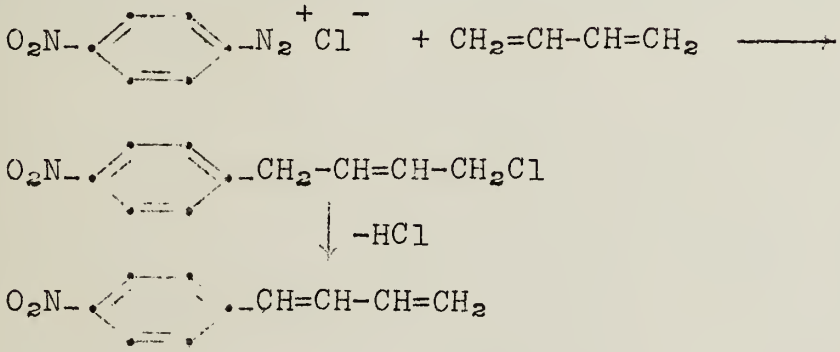
a. α-Cyano stilbenes

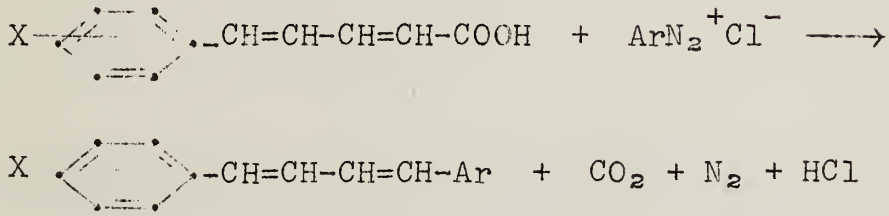
(4) 

b. α-Acetyl stilbenes

(4) 

4. Aryl-1,3-butadienes

(20,21) 

(6,7,8,9,10,19) 

5. Aryl maleic acids

(1,24) $CH_3OOC-CH=CH-COOCH_3 + ArN_2^+Cl^-$ ⟶

$CH_3OOC-CH=C(Ar)-COOCH_3$

$+ N_2 + HCl$

6. Styrenes

(22,23) $ClCH{=}CCl_2 + ArN_2^+Cl^- \longrightarrow ArCHClCCl_3 \longrightarrow$

$ArCCl{=}CCl_2$

(22,23) $HC{\equiv}CH + ArN_2^+Cl^- \longrightarrow ArCH{=}CHCl + N_2 + HCl$

7. Indirect Syntheses: By appropriate treatment of the initial Meerwein reaction product, 4,4'-disubstituted biphenyls (from

bibenzyls (from styrenes by reduction), γ-arylpropylamines (from Ar-CH=CH-CN by reduction), etc., may be prepared. Notable among syntheses utilizing the Meerwein reaction as a key step are the phenanthridine synthesis of Braude and Fawcett (25) and the <u>lin</u>-quaterphenyl synthesis of Bergmann and Weizman (10).

<u>Mechanism</u>: Both free radical and ionic mechanisms have been proposed for the Meerwein reaction.

1. <u>Free radical</u> Koelsch and Boekelheide (19) have proposed the following scheme to account for the products and orientation of the reaction.

(1.) $ArN_2^+ + CH_3COO^- \rightleftharpoons ArN{=}N{-}OCOCH_3 \longrightarrow Ar^\cdot + N_2 + CH_3COO^\cdot$

(2.) $Ar^\cdot + R{-}CH{=}CH{-}R' \longrightarrow Ar{-}CHR{-}\dot{C}HR'$ (A)

(3.) $Ar{-}CHR{-}\dot{C}HR' + Cu^{++} \longrightarrow Ar{-}CHR{-}\overset{+}{C}HR' + Cu^+$

(3a.) $Cu^+ + CH_3COO^\cdot \longrightarrow Cu^{++} + CH_3COO^-$

(4.) $Ar{-}CHR{-}\underset{+}{C}HR' + Cl^- \longrightarrow Ar{-}CHR{-}\underset{Cl}{C}H{-}R'$

(4a.) $Ar{-}CHR{-}\underset{+}{C}HR' \longrightarrow H^+ + Ar{-}\underset{R}{C}{=}CHR'$

α-Coupling with cinnamic acid derivatives was explained on the assumption that the free radical formed initially (Equation 2,A) would be more stable than the alternative structure because of resonance of the free electron into the phenyl group; and similarly, β-coupling with acrylic acid was explained on the assumption that the free radical formed initially could be stabilized by resonance of the free electron on the α-carbon ($ArCH_2{-}CH{-}COOR$) into the carboxyl group. These views were shared by Dhingra and Mathur (14).

2. Ionic The proponents for the ionic mechanism (11, 12, 13) point out that the orientation observed in the Meerwein reaction in many instances parallels that of ionic addition of HBr rather than the peroxide-catalyzed, free radical addition. Brunner and Perger (12) have proposed that the cupric chloride functions simply as a halogen carrier and have successfully substituted pyridine for cupric chloride in one instance. The beneficial effect of acetone has been ascribed to its function as a halogen carrier through the initial formation of chloroacetone.

The arguments for each theory fail to exclude the possibility of the alternate mechanism, and it seems probable that, in view of the number of side-reactions which invariably accompany the Meerwein reaction, the reaction is exceedingly complex and may involve both radical and ionic mechanisms.

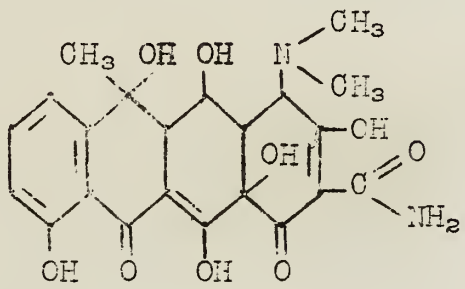
References

1. H. Meerwein, E. Büchner and K. van Emster, J. Prakt. Chem., 152, 237 (1939)
2. G. A. R. Kon, J. Chem. Soc., 224 (1948)
3. D. M. Brown and G. A. R. Kon, ibid., 2147 (1948)
4. P. L'Ecuyer and C. A. Olivier, Can. J. Research, 27B, 689 (1949)
5. P. L'Ecuyer, F. Turcotte, J. Giguere, C. A. Olivier and P. Roberge, ibid., 26B, 70 (1948)
6. P. L'Ecuyer and F. Turcotte, ibid., 25B, 575 (1947)
7. F. Bergmann and Z. Weinberg, J. Org. Chem., 6, 134 (1941)
8. G. B. Bachman and R. I. Hoaglin, ibid., 8, 300 (1943)
9. F. Bergman, J. Weizman and D. Schapiro, ibid., 9, 408 (1944)
10. F. Bergmann and J. Weizman, ibid., 9, 415 (1944)
11. F. Bergmann and D. Schapiro, ibid., 12, 57 (1947)
12. W. H. Brunner and H. Perger, Monatsh., 79, 187 (1948)
13. W. H. Brunner, ibid., 82, 100 (1951)
14. D. R. Dhingra and K. B. L. Mathur, Ind. Chem. Soc. J., 24, 123 (1947)
15. J. Rai and K. B. L. Mathur, ibid., 24, 383 (1947)
16. J. Rai and K. B. L. Mathur, ibid., 24, 413 (1947)
17. R. C. Fuson and H. G. Cooke, Jr., J. Am. Chem. Soc., 62, 1180 (1940)
18. C. F. Koelsch, ibid., 65, 57 (1943)
19. C. F. Koelsch and V. Boekelheide, ibid., 66, 412 (1944)
20. E. C. Coyner and G. A. Ropp, ibid., 70, 2283 (1948)
21. G. A. Ropp and E. C. Coyner, Org. Syn. 31, 80 (1951)
22. E. Müller, Angew. Chem., 61, 179 (1949)
23. E. Müller, Ueber die Einwirkung von aromatischen Diazoverbindungen auf aliphatische ungesättigte Verbindungen, PB 737, Office of Technical Services, Department of Commerce, Washington, D. C.
24. E. C. Taylor, Jr. and E. J. Strojny, Unpublished Work
25. E. A. Braude and J. S. Fawcett, J. Chem. Soc., 3113 (1951)

THE STRUCTURE OF TERRAMYCIN

Reported by Charles King October 3, 1952

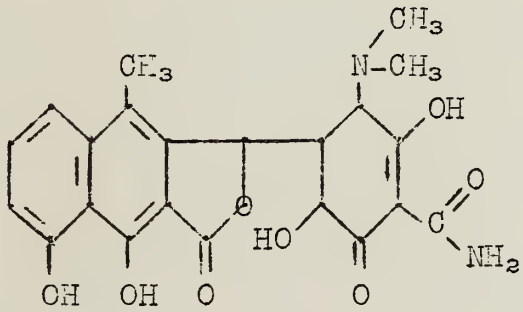
Terramycin,[1] $C_{22}H_{24}N_2O_9$, a new broad-spectrum antibiotic, has recently been assigned the structural formula I:



I

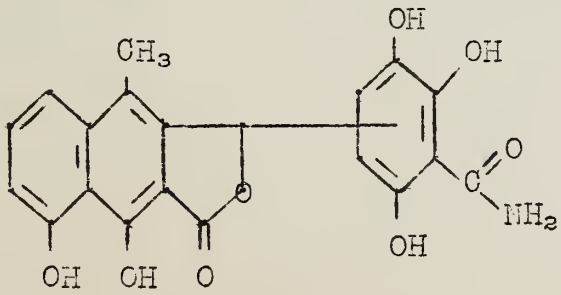
Aromatization of terramycin yields naphthacene, and demonstrates the presence of this ring system in the molecule. Structure I is consistent with certain products identified from both acid and alkaline degradation of terramycin.[2-8]

Treatment of terramycin with 1.5 N aqueous hydrochloric acid yields, with dehydration and rearrangement, α- and β-apoterramycin which are regarded as stereoisomers of structure II:



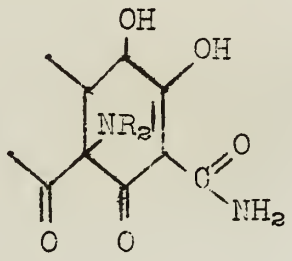
II

More vigorous treatment with dilute hydrochloric acid yields terrinolide, III:



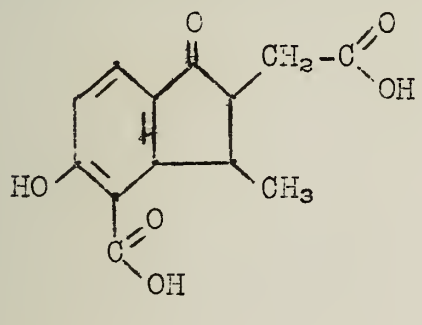
III

The infrared absorption spectrum of terramycin shows no absorption between 5 and 6μ, and indicates that the phthalide carbonyl in II and III is derived from a highly conjugated or enolized carbonyl group. Moreover this carbonyl must be incorporated in an actual or potential β-dicarbonyl system. The alternative formula IV is ruled out on the basis that the pK_a of the dimethylamino group is not appreciably altered in the transformation to the apoterramycins.



IV

Alkaline degradation of terramycin yields products V-IX, which appear to be consistent with I.



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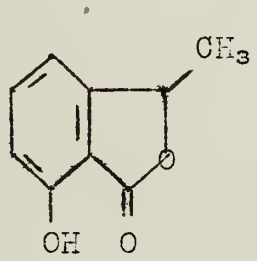

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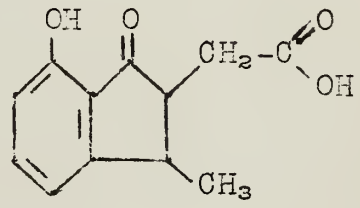
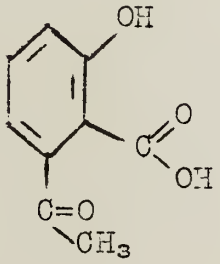
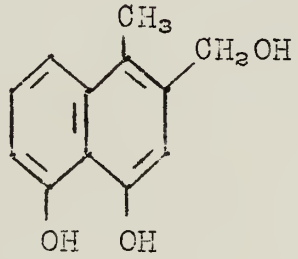


VII



VIII



IX

Bibliography

1. Finlay, A. C., Hobby, G. L., P'an, S. Y., Regna, P. P., Routiew, J. B., Seeley, D. B., Shull, G. M., Sobin, B. A., Solomons, I. A., Vinson, J. J., and Kane, J. H., Science, 111, 85 (1950).
2. Hochstein, F. A., Stephens, C. R., Conover, L. H., Regna, P. P., Pasternack, R., Brunings, K. J., and Woodward, R. B., J. Am. Chem. Soc., 74, 3708 (1952).
3. Hochstein, F. A., Stephens, C. R., Gordon, P. N., Regna, P. P., Pilgrim, J. J., Brunings, K. J., and Woodward, R. B., J. Am. Chem. Soc., 74, 3707 (1952).
4. Hochstein, F. A., Regna, P. P., Brunings, K. J., and Woodward, R. B., J. Am. Chem. Soc., 74, 3706 (1952).
5. Pasternack, R., Regna, P., Wagner, R., Bavley, A., Hochstein, F. A., Gordon, P., and Brunings, K., J. Am. Chem. Soc., 73, 2400 (1951).
6. Pasternack, R., Conover, L. H., Bavley, A., Hochstein, F. A., Hess, G. B., and Brunings, K. J., J. Am. Chem. Soc., 74, 1929 (1952).
7. Hochstein, F. A., and Pasternack, R., J. Am. Chem. Soc., 73, 5006 (1951).
8. Kuhn, R., and Dury, K., Ber., 84, 848 (1951).

IRON BIS-CYCLOPENTADIENYL

Reported by B. L. Van Duuren October 3, 1952

In an attempt to prepare organochromium compounds from phenylmagnesium bromide and chromic chloride Bennett and Turner[1] obtained an almost quantitative yield of diphenyl formed by the coupling reaction:

$$2C_6H_5MgX + MX_2 \rightarrow C_6H_5C_6H_5 + 2MgX_2 + M \qquad (a)$$

Later workers [2,3] have shown that unstable organometallic compounds are probably intermediates in the coupling reaction:

$$2R{\cdot}Mg{\cdot}X + MX_2 \rightarrow R{\cdot}M{\cdot}R + 2MgX_2 \qquad (b)$$

$$R{\cdot}M{\cdot}R \rightarrow R{\cdot}R + M \qquad (c)$$

Numerous attempts to prepare and isolate these organometallic compounds have been made, without success.

In 1951 Kealy and Pauson[4] attempted the preparation of the hydrocarbon fulvalene[5], I, from cyclopentadienylmagnesium bromide and anhydrous ferric chloride.

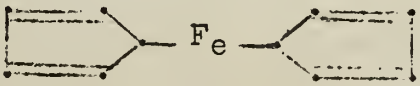
I

Instead of the expected coupling product they obtained a new organo-iron compound which analysed for $C_{10}H_{10}Fe$. They considered this compound to be iron bis-cyclopentadienyl formed by reaction b, above.

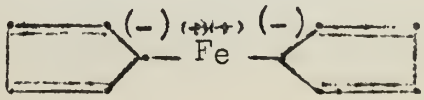
Less than a month before this discovery was reported Miller and others[6] reported that a yellow crystalline compound, $C_{10}H_{10}Fe$, is obtained by passing cyclopentadiene over reduced iron in the form of synthetic ammonia catalyst at 300° and atmospheric pressure in the presence of nitrogen.

The authors of both papers realized that this compound was exceptional: it is stable to heat, water, alkali and concentrated hydrochloric acid. It is volatile in steam or ethanol and could be readily sublimed.

Kealy and Pauson[4] wrote structure II for the compound and suggested that it acquires a negative charge, becomes aromatic and resonance forms such as III participate.



II



III

Miller and coworkers[6] also suggested structure II by analogy to potassium cyclopentadienyl[7].

According to Fischer and Pfab[8] iron bis-cyclopentadienyl is a penetration complex. These are stable complexes in which the valence electrons of the central atom form common shells with the electron pairs binding the groups eg. the $PtCl_6^{2-}$ and $Fe(CN)_6^{4-}$ ions[9]. In the compound under discussion the effective atomic number of the iron atom is 36 i.e. a krypton configuration as in the ferrocyanide ion. These authors cited the diamagnetic properties of the compound as proof for this type of structure. They obtained evidence for an iron bis-cyclopentadienyl cation which they formulated as IV.

$$\left[{}^{(-)}(C_5H_5) \rightleftarrows Fe^{3(+)} \rightleftarrows (C_5H_5)^{(-)} \right]^{(+)}$$

IV

An important contribution as to the nature of the iron compound was made by Woodward and coworkers[10,11]. These workers also obtained evidence for a cation, $[(C_5H_5)_2Fe]^{(+)}$, and attributed the blue color, observed by Kealy and Pauson[4], which accompanied solution of the compound in sulphuric or nitric acid to this cation. The cation was isolated as a crystalline tetrahydrogallate, $C_{10}H_{10}FeGaCl_4$. They noted also that the substance was diamagnetic and that the infrared absorption spectrum indicated a single sharp band at 3.25 μ. From this result it was concluded that there is only one type of C-H bond in the molecule and structure V was suggested. They also proposed the name ferrocene for this compound.

V

This molecule consists of two rings each containing five equivalent C-H groups so that the compound might be expected to behave as an aromatic substance. The idea of aromaticity was probably also in the minds of Kealy and Pauson[4] although they did not elaborate on it.

Woodward and coworkers[11] showed that the compound does not exhibit any properties typical of polyolefinic substances. With acetyl chloride a diacetyl derivative was obtained and with β-chloropropionyl chloride bis-β-chloropropionylferrocene and bis-acryloylferrocene were obtained. Oxidation of the diacetyl

derivative afforded a dicarboxylic acid. Substitution reactions typical of aromatic systems eg. the preparation of nitro- and bromo-derivatives could not be carried out in view of the ready oxidation to the cation by such reagents.

The infrared absorption spectra of the ferrocene derivatives showed a marked resemblance to those from benzene. From the fact that pK_1 for ferrocene dicarboxylic acid is very similar to pK for benzoic acid, Woodward concluded that the ring carbon atoms and thus also the iron atom in ferrocene are substantially electricall neutral.

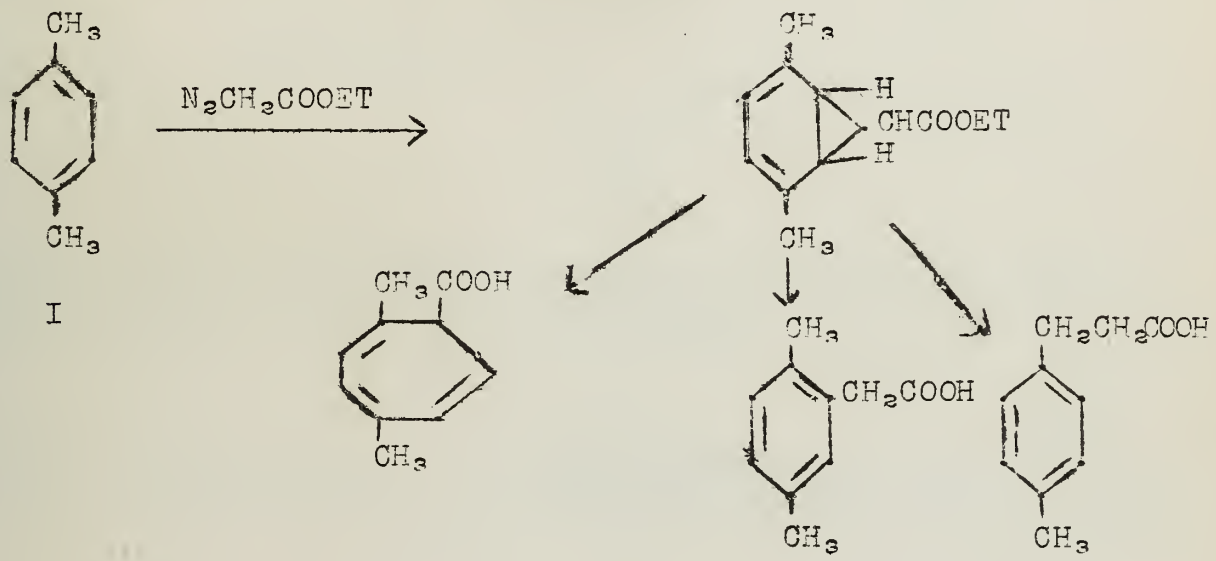
BIBLIOGRAPHY

1. G. M. Bennett and E. E. Turner, J. Chem. Soc., 105, 1057 (1914
2. E. Krause and B. Wendt, Ber., 56, 2064 (1923).
3. J. Krizewski and E. E. Turner, J. Chem. Soc., 115, 559 (1919).
4. T. J. Kealy and P. L. Pauson, Nature, 168, 1039 (1951).
5. R. D. Brown, Nature, 165, 566 (1950).
6. S. A. Miller, J. A. Tebboth and J. F. Tremaine, J. Chem. Soc., 1952, 632.
7. J. Thiele, Ber., 34, 68 (1901).
8. E. O. Fischer and W. Pfab, Zeits, Nature, 7, 377 (1952).
9. W. Hückel, Structural Chemistry of Inorganic Compounds, Elsevier Publishing Co., Inc., New York, 1950, Vol. I., p. 58.
10. G. F. Wilkinson, M. Rosenblum, M. C. Whiting and R. B. Woodward J. Am. Chem. Soc., 74, 2125 (1952).
11. R. B. Woodward, M. Rosenblum and M. C. Whiting, J. Am. Chem. Soc., 74, 3458 (1952).

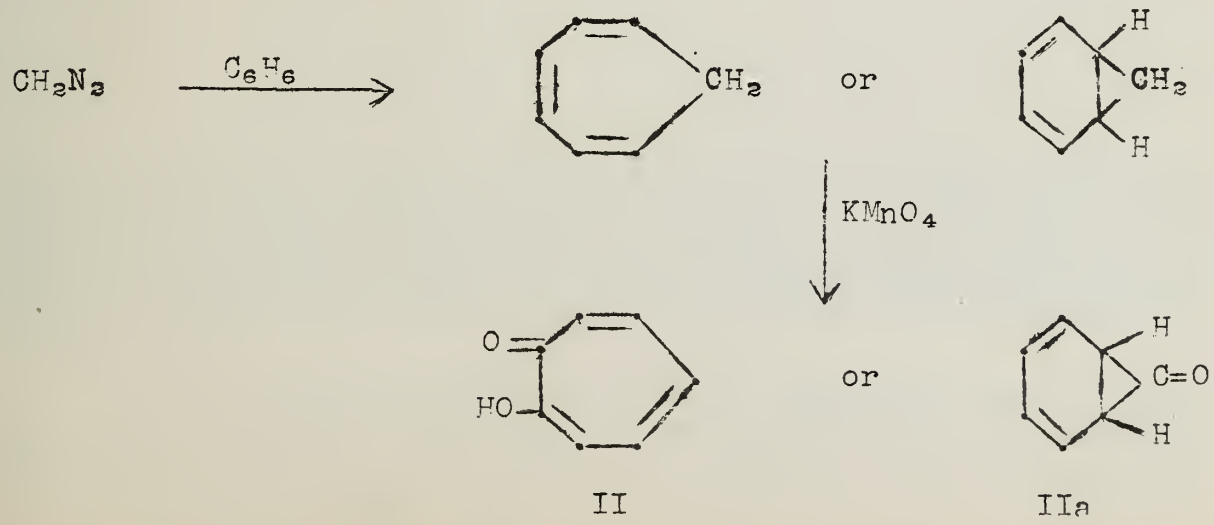
THE VICINAL ADDITION OF CERTAIN REAGENTS TO AROMATIC SYSTEMS

Reported by William S. Friedlander October 10, 1952

In 1885 Buchner and Curtius in searching for a suitable solvent for diazoacetic ester found that it attacked such aromatic compounds as benzene and toluene to yield the corresponding heptatriene carboxylic acids [1]. Further work has shown that diazoacetic ester will add to benzene derivatives with unsubstitued ortho positions to yield norcaradiene dicarboxylic acids, which rearrange with heat and alkali to cycloheptatriene carboxylic acids, the corresponding phenylacetic acid, or a substituted phenylpropionic acid. This is shown with p-xylene (I).

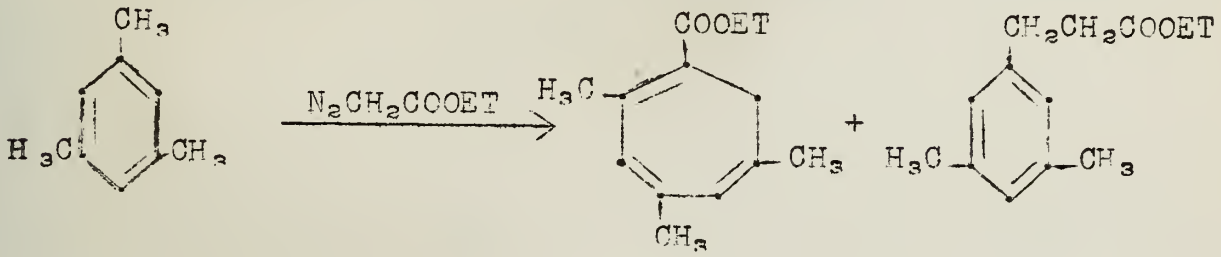


Doering and co-workers[5,6] have used diazomethane under photochemical conditions to produce tropolone (II) from benzene and tropone from anisole.

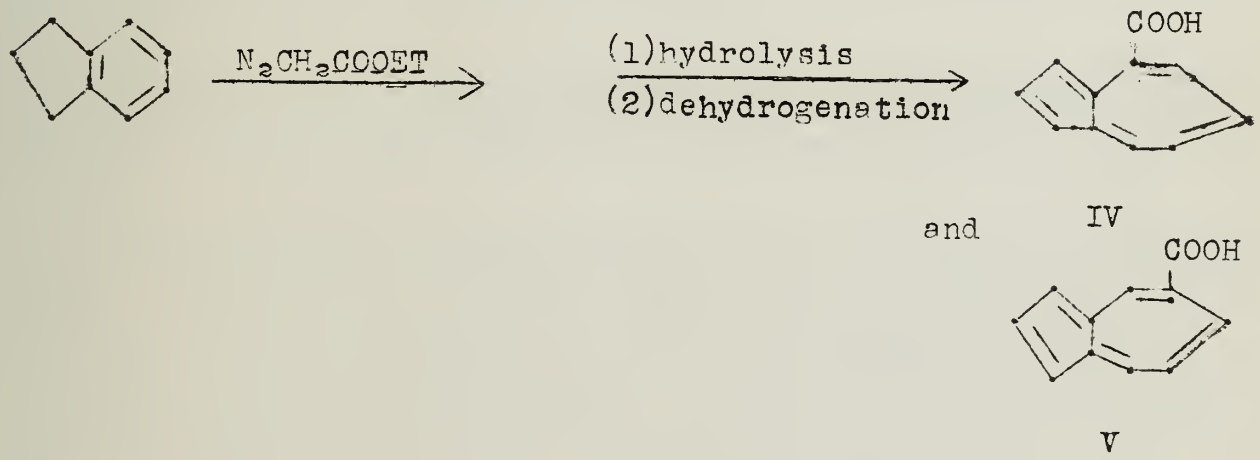


This method does not exclude IIa as a possible structure. The yield of II, isolated as the copper salt, is 1%. Bartels-Keith and Johnson (7) have used ethyl diazoacetate to synthesize tropolone carboxylic acid from veratrole.

In the case of benzene derivatives which have no o-unsubstituted positions such as mesitylene (III) or durene, only rearrangement products are isolated.



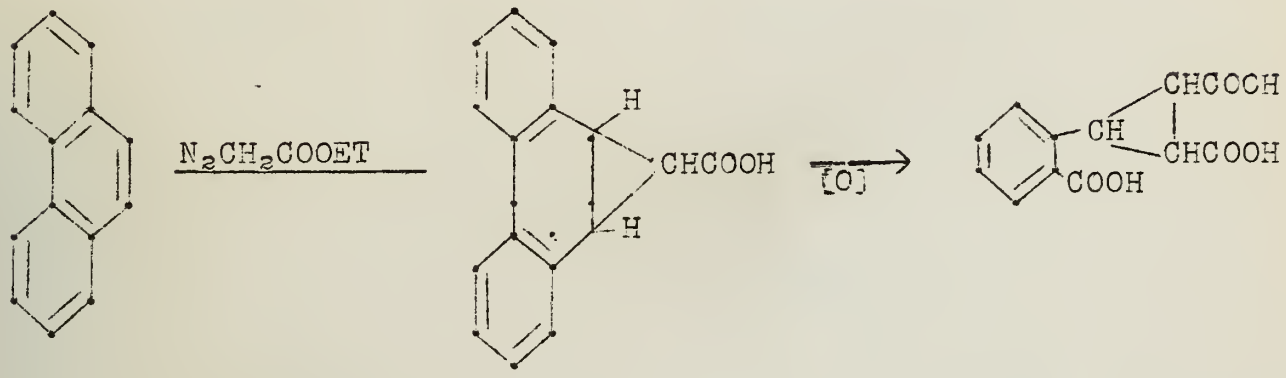
Plattner[4] has used the reaction of ethyl diazoacetate to produce azulene carboxylic acids (IV,V) from indane.



These facts led Buchner to formulate a rule[2]: <u>Condensation of ethyl diazoacetate with an aromatic hydrocarbon always involves addition to a non-substituted carbon atom. If the nature of the hydrocarbon preculdes this type of addition, a rearrangement product of the bicyclic ester is obtained rather than the bicyclic ester itself</u>.

Reaction of diazoacetic ester with <u>condensed</u> ring systems produces very stable norcaranes. For example, the 9,10-dihydophenathr-9,10-yleneacetic acid (VI) produced from phenanthrene (V) can be heated for 6 hours with sodium hydroxide in ethylene

glycol at 170°c and then can be recovered unchanged[2]. The structure of Vi was proved by degradation to the known 1-(2'-carboxyphenyl)-2,3-cyclopropanedicarboxylic acid (VII).

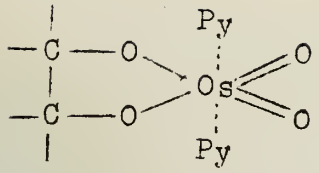


V VI VII

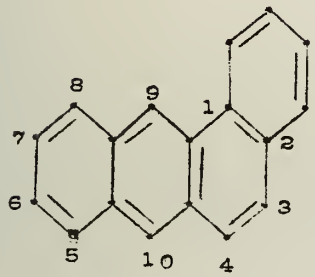
Other workers have shown that diazoacetic ester will add to the 1,2-bond of naphthalene[1], the 1,2-bond of anthracene[3], and the 4,5 (or 9,10) bond of pyrene[3]. In all cases the product (usually in low yield) is a norcarane carboxylic acid as illustrated with phenanthrene (V).

The stability of the norcaranes formed from condensed ring systems is of some interest. It may be that the cyclopropane ring is conjugated with the remaining aromatic bonds of the [illegible] system[8].

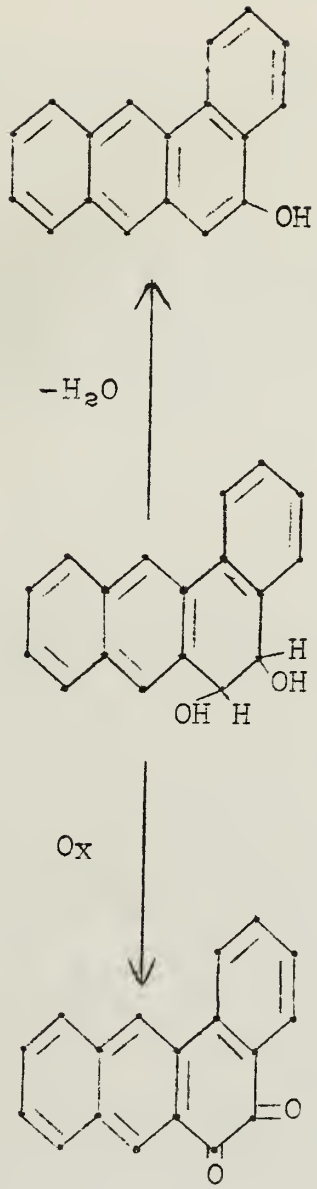
Another reagent which attacks aromatic systems in a vicinal manner is osmium tetroxide. Criegee[9] has shown that the reaction between this reagent and double bonds is quantitative and that addition to aromatic bonds of high order also occurs. Badger has used it to determine the amount of "double-bond character" present in carcinogenic agents[11]. When the addition of osmium tetroxide is carried out in pyridine, the first product is a colored, cyclic osmate ester (complexed with pyridine) (VIII). Hydrolysis of this produces <u>cis</u> 1,2-diols, which can be oxidized to o-quinones or dehydrated to give phenols. This reaction is shown with 1,2-benzanthracene (IX).



VIII



IX



Cook and Schoental[11] have extended this reaction to many carcinogenic hydrocarbons such as the various methyl substituted 1,2-benzanthracenes, chrysene and pyrene. These oxidations to diols represent the first successful chemical oxidations of benzanthracene type hydrocarbons in positions other than the reactive meso(9,10) position of the anthracene unit which is present.

Wibaut[12] has done extensive work with the addition of ozone to aromatic systems. As with osmium tetroxide and diazoacetic ester the initial attack comes at the position having the highest bond order. Generally, the reagent has been most useful in structure determination. However, Vollman has used it to prepare 4-formyl-5-carboxyphenanthrene from pyrene[13], and Newman[15] has

used it (going via Vollman's compound) to prepare 4,5-dimethylphenathrene.

The theoretical considerations relating to the addition to aromatic systems of these three reagents are quite interesting. As has been pointed out in the case of osmium tetroxide and ozone, the oxidation occurs at the bond which has the lowest "localization energy" for the π electrons. This position is almost never the same for normal electrophilic attack particularly for the larger condensed aromatic systems. The case of pyrene is perhaps the most striking of all. It normally undergoes electrophilic substitution at the 1,3,6, and 8 positions, but ozonolysis goes first at the 4,5 then 9,10 positions[14] and reaction with osmium tetroxile goes at either the 4,5 or 9,10 position[10].

REFERENCES

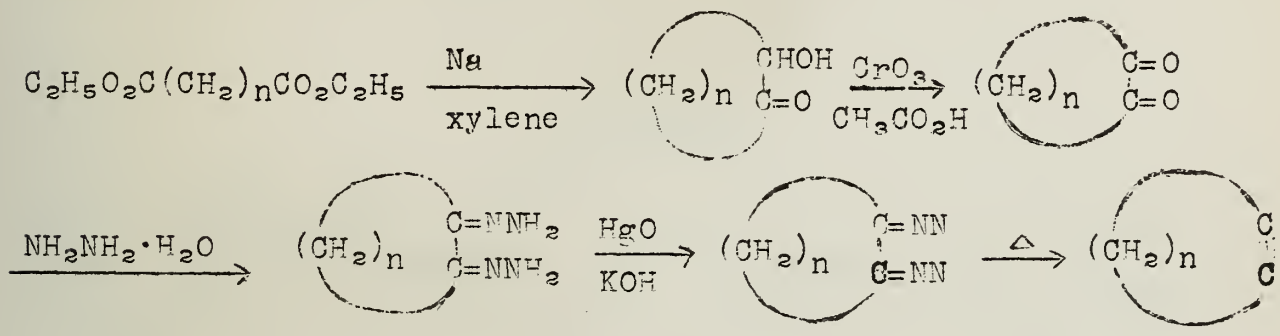
1. E. Buchner and S. Hediger, Ber. 36, 3502 (1903).
2. N. L. Drake and T. R. Sweeney, J. Org. Chem., 11, 67 (1946).
3. G. M. Badger, J. W. Cook and A. R. Gibb, J. Chem. Soc., 1951, 3456.
4. P. A. Plattner, A. Furst, A. Müller and A. R. Somerville, Helv. Chim. Acta, 34, 971 (1951).
5. W. von E. Doering and L. H. Knox, J. Am. Chem. Soc., 72, 2305 (1950).
6. W. von E. Doering and F. L. Detert, ibid, 73, 876 (1951).
7. J. R. Bartels-Keith and A. W. Johnson, Chem. and Ind., 1950, 677.
8. R. V. Volkenburgh, K. W. Greenlee, J. M. Derfer, and C. E. Boord, J. Am. Chem. Soc., 71, 3595 (1949).
9. R. Criegee, B. Marchand and H. Wannowius, Ann. 550, 99 (1942).
10. G. M. Badger, J. Chem. Soc., 1949, 456.
11. J. W. Cook and R. Schoental, J. Chem. Soc., 1948, 170.
12. J. P. Wibaut, Comptes Rendus de la Quinzieme Conference, Union International de Chimie Pure et Appliquee 1949, p. 79.
13. Vollman, et al, Ann. 531, 1 (1937).
14. G. M. Badger, Rec. Trav. Chim., 71, 468 (1952).
15. M. S. Newman and H. S. Whitehouse, J. Am. Chem. Soc., 71, 3664 (1949).

THE SYNTHESIS AND PROPERTIES OF CYCLOÖLEFINS CONTAINING NINE AND TEN CARBONS

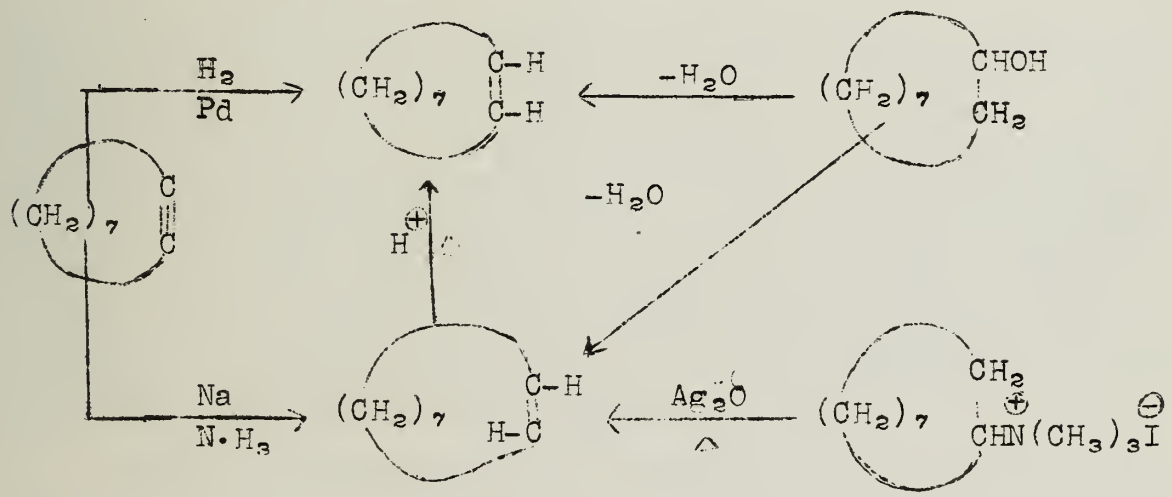
Reported by Elliott E. Ryder October 10, 1952

The report of the synthesis and properties of eight membered carbocycles containing olefinic and acetylenic linkages[1,2,3] brought about an increased interest in similar compounds containing large rings.

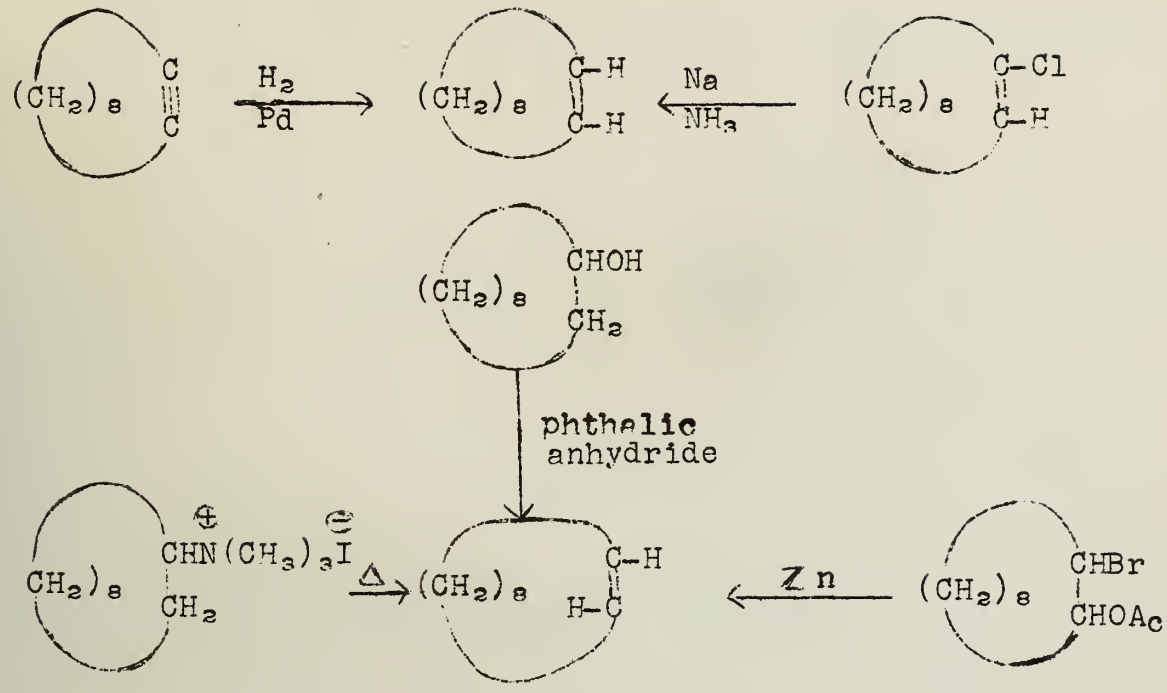
Cyclononyne and cyclodecyne were prepared in the following manner in about ten percent yield[4,5].



The synthesis of cis-and trans-cyclononene was carried out by various methods.



Cis-and trans-cyclodecene were prepared similarly.



It is interesting to compare the properties of the eight, nine, and ten membered cycloölefins. In strainless acyclic compounds containing multiple bonds there is a decrease in refractive index in the order alkyne, cis-alkene, trans-alkene. In the eight membered cyclic system the positions of the cis-and trans-olefins are reversed, due presumably to the relatively great strain of the trans modification. In the nine membered series the cis and trans forms have very nearly the same refractive index, indicating the presence of a small amount of strain in the trans isomer. Cis-and trans-cyclodecene have values which vary considerably in the order which would be predicted from a consideration of acyclic compounds, thus implying that essentially no strain exists in the ten membered system.

Another comparison of the relative amounts of strain in these carbocycles is given by a study of the dehydration of the corresponding alcohols. Cycloöctanol gives only cis-cycloöctene while cyclononanol gives a mixture of the cis and trans isomers. Cyclodecanol yields only trans-cyclodecene.

A final criterion by which one may judge the relative stability of isomers is in the reaction with phenyl azide[1]. Trans-cycloöctene reacts with this reagent within a few moments, considerably faster than the cis-form. Trans-cyclononene gives a crystalline adduct within a few hours while the cis isomer fails to react. Neither modification of cyclodecene gives any reaction,

as might be expected.

It is of interest to note that by a study of structural models it is seen that enantiomorphs of trans-cyclononene should exist.

BIBLIOGRAPHY

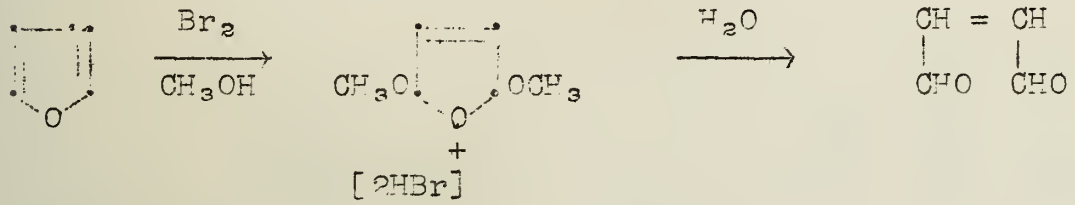
1. K. Ziegler and H. Wilms, Ann., 567, 1 (1950).
2. L. E. Craig, Chem. Revs., 49, 103 (1951).
3. N. A. Domnin, J. Gen. Chem. (U.S.S.R.), 8, 851 (1938); C.A., 33, 1282 (1939).
4. A. T. Blomquist, R. E. Burge, Jr., A. C. Sucsy, J. Am. Chem. Soc., 74, 3636 (1952).
5. A. T. Blomquist, L. H. Liu, J. C. Bohrer, J. Am. Chem. Soc., 74, 3643 (1952).

THE ALKOXYLATION OF SIMPLE FURANS AND RELATED REACTIONS

Reported by Paul L. Cook October 17, 1952

Introduction

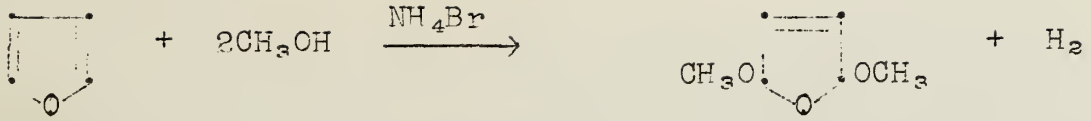
The addition of alkoxy groups to the α-carbons of furans results in the formation of stable 2,5-dialkoxy-2,5-dihydrofurans The importance of these addition products is illustrated by the fact that they can be easily hydrolyzed to the corresponding unsaturated 1,4-dicarbonyl compounds which often are accessible only with difficulty by other methods. This alkoxylation procedure is demonstrated in the following equation:[1]



Alkoxylation

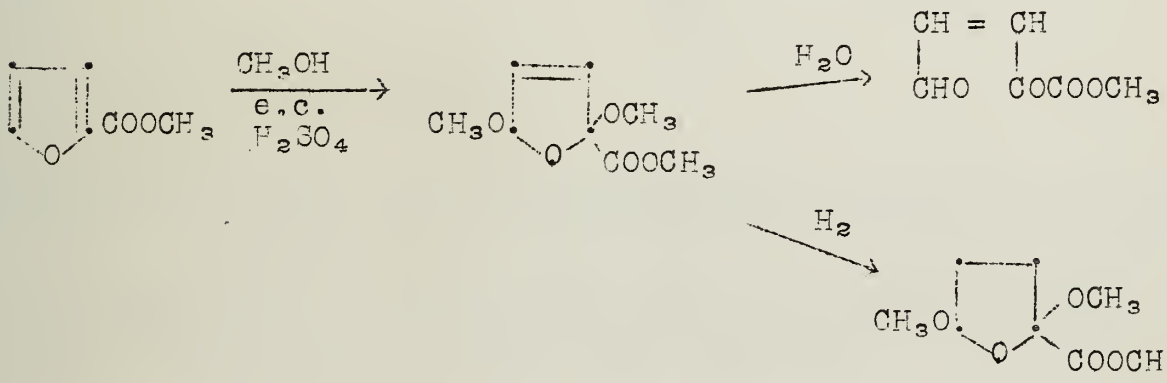
Alkoxylation of furans was accomplished in 1937 by Meinel[2], and by Clauson-Kaas and his associates[3] with bromine in alcohol at low temperature in the presence of potassium acetate which neutralized the hydrogen bromide formed by the reaction. However, there were certain limitations to this reaction. This method could not be used to alkoxylate furans which had an electronegative substituent in the α position, such as furoic acid, ethyl furoate, ethyl furylacrylate, acetyl furan and 2,5-dibromofuran. One exception was furfural[3], but in this case dimethoxydihydrofurfural dimethyl acetal was formed, so that probably acetalization or semi-acetalization had taken place prior to methoxylation. Methyl 2-furoate was also methoxylated[4], but the product was obtained in an impure state and in a yield of only 12 per cent. Another limitation of this reaction was the fact that the dialkoxydihydrofuran was contaminated with a small amount of some halogen-containing impurity from which hydrogen bromide could be generated. This impurity had an adverse effect upon the stability of the acid-sensitive dialkoxyfuran.

Recently Clauson-Kaas has developed a methoxylation method which is simpler and cheaper than the one above and which gives a halogen-free product[5,6]. Furan is mixed with a methanolic solution of ammonium bromide and the mixture is electrolyzed. At the cathode hydrogen and ammonia are formed, and at the anode bromine is produced. The bromine reacts immediately with furan and methanol to give dimethoxydihydrofuran and hydrogen bromide. Ammonium bromide is regenerated from the ammonia at the cathode and the hydrogen bromide. The net equation for the process is:



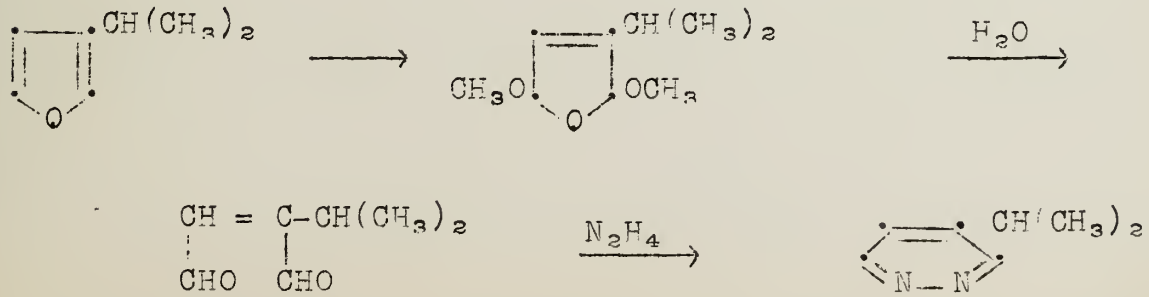
The yield of dimethoxydihydrofuran is 73%, about 10% higher than that by the other method.

This new electrolytic process has also made possible the methoxylation of a furan with a negative α substituent. A 68% yield of analytically pure dimethoxydihydro-2-furoic acid methyl ester was obtained by electrolyzing a mixture of methyl furoate, methanol and sulfuric acid.



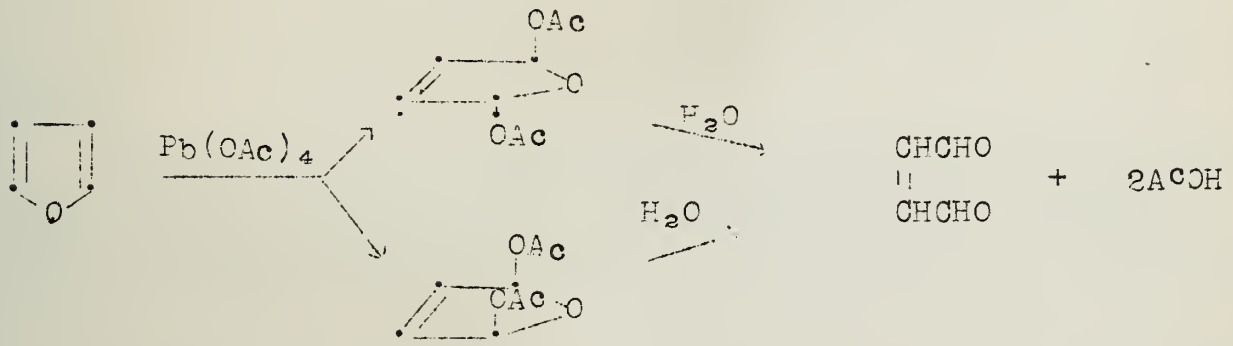
It is possible that this method may be extended to other furans with a negative substituent.

The electrolytic method of alkoxylation has also been tried on three β-substituted furans, namely, β-isopropylfuran, 4-isopropyl-2-furaldehyde dimethyl acetal, and methyl 4-isopropyl-2-furoate. The product from the alkoxylation of β-isopropylfuran was hydrolyzed and the hydrolysis product treated with hydrazine to give 4-isopropylpyridazine.



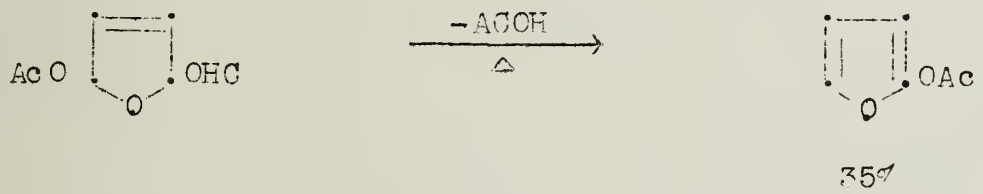
Acetoxylation

The addition of two acetoxy groups to furan was reported in 1947 by Clauson-Kaas[3,7]. The reaction was carried out both with lead tetraacetate and with bromine in acetic acid, the better yield being obtained with the lead salt. In a recent paper[8] the same author reports an improved method of acetoxylation, again using lead tetraacetate. He also succeeded in isolating the *cis* and *trans* isomers of 2,5-diacetoxy-2,5-dihydrofuran.

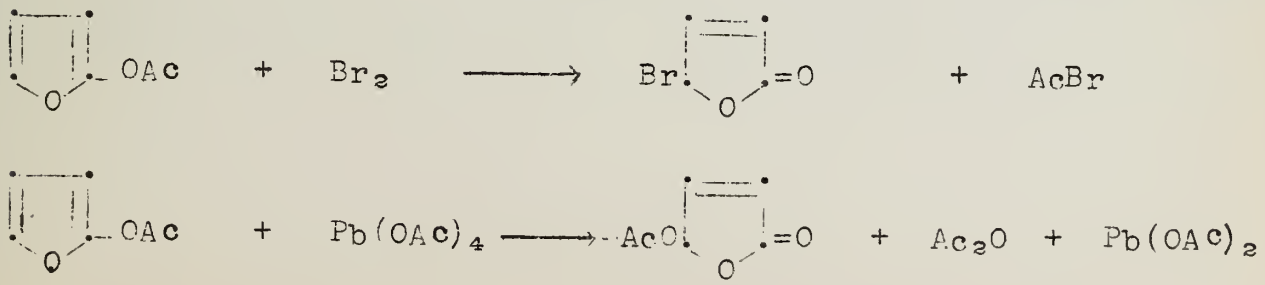


2,5-Diproprionoxy- and 2,5-dibutyroxy-2,5-dihydrofurans were also prepared from furan and the corresponding lead tetracyloxalates.

The discovery was also made that pyrolysis of 2,5-diacetoxy-2,5-dihydrofuran lead to 2-acetoxyfuran[9], hitherto unknown. The yield of this reaction is low (35%), however.

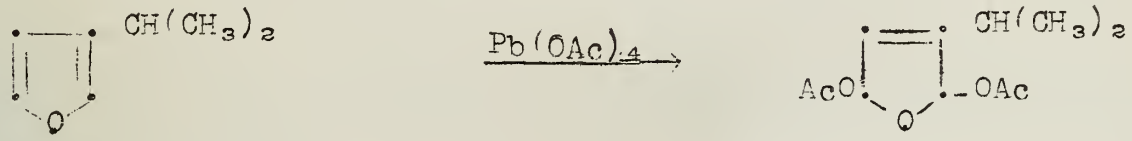


2-Acetoxyfuran has been used as an intermediate in the preparation of certain 5-substituted 2-oxo-2,5-dihydrofurans.



The acetoxylation of furans with Pb(OAc)4 is not nearly as

general for furans as is alkoxylation. Clauson-Kaas, Limborg and Fakstorp[10] failed to acetoxylate furoic acid and ethyl furoate by this method. Attempts to acetoxylate other α-substituted furans such as silvan, furfuryl acetate, furfural diacetate and 2-acetylfuran have also met with failure[11]. However, β-isopropylfuran was acetoxylated with lead tetraacetate in fair (54%) yield.



Summary

Improved methods of alkoxylation and acetoxylation of furans have recently been developed. Although alkoxylation methods are quite general for both α- and β- substituted furans, acetoxylation has been successful only with furan itself and β-isopropylfuran.

REFERENCES

1. N. Clauson-Kaas, F. Limborg, and J. Fakstorp, Acta Chem. Scand., 2, 109 (1948).
2. K. Meinel, Ann. 516, 231 (1935).
3. N. Clauson-Kaas, Kgl. Danske Videnskab Selskab, Mat.-fys. Midd., 24, 6 (1947).
4. D. G. Jones and Imperial Chemical Industries Ltd, Brit. patent 595041; C. A., 42, 2992 (1948).
5. N. Clauson-Kaas (to Kimisk Vaerk Koge AIS). Belg. patent 500356 (1951).
6. N. Clauson-Kaas, F. Limborg and K. Glens, Acta Chem. Scand., 6, 531 (1952).
7. N. Clauson-Kaas, Acta Chem. Scand., 1, 379 (1947).
8. N. Elming and N. Clauson-Kaas, Acta Chem. Scand., 6, 535 (1952).
9. N. Clauson-Kaas and N. Elming, Acta Chem. Scand., 6, 560 (1952).
10. N. Clauson-Kaas, F. Limborg and J. Fakstorp, Acta Chem. Scand. 2, 109 (1948).
11. N. Elming, Acta Chem. Scand., 6, 578 (1952).

ATTEMPTED SYNTHESES OF SIMPLE PENTALENES

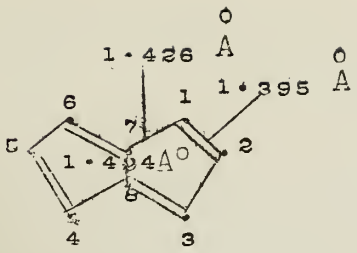
Reported by John R. Demuth October 17, 1952

Introduction: Pentalene is as yet an unknown hydrocarbon composed of two fused cyclopentadiene rings. Its structure, the numbering system used in naming pentalene derivatives, and the carbon to carbon distances calculated on the basis of theoretical considerations[17,18] are shown in formula I. Armit and Robinson[1] first postulated pentalene as a possible aromatic type, and with the recent surge of interest in non-benzenoid aromatic compounds, pentalene and its derivatives have been the subject of a number of investigations.

Whether pentalene will show aromatic or olefinic behavior in its reactions is a matter of controversy. In a theoretical paper in which he used the molecular orbital theory to calculate pi electron densities, bond orders and bond lengths, Brown[17] predicts that once formed, pentalene should be a reasonably stable molecule. Electrophilic attack should occur at carbon number two, and nucleophilic and free-radical attack at carbon one, since position one is the point of lowest electron density and of highest free valency. Craig and Maccoll[19,20], on the other hand, using the valence bond method have come to the conclusion that "pentalene should show marked unsaturation and unequal carbon-carbon distances." The meager experimental data available indicate that perhaps the latter conclusions are the correct ones.

Types of Pentalene Compounds:

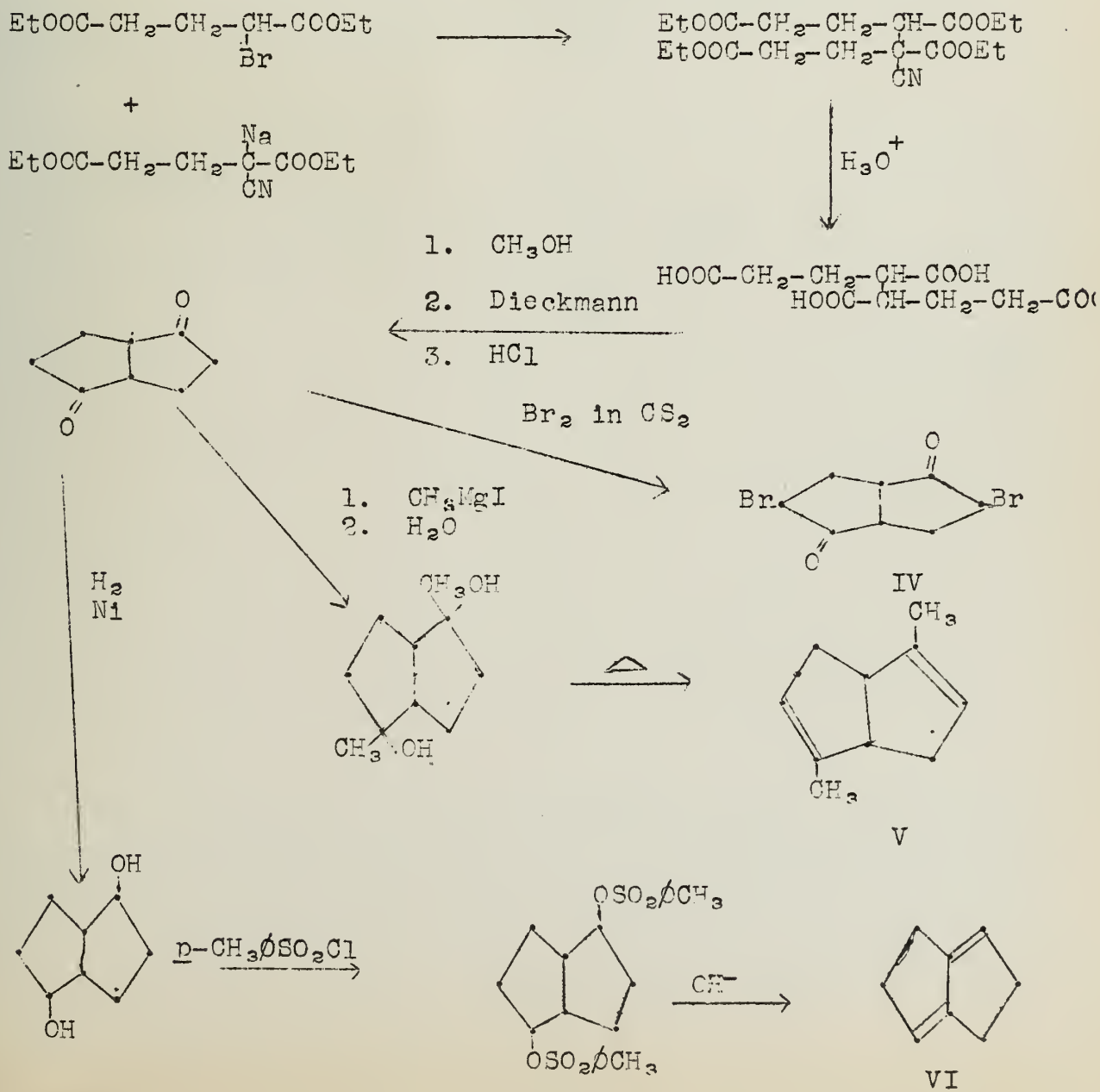
A. Pentalene, Bicyclo[3.3.0]octatetraene. The first attempt to synthesize pentalene was made by Barrett and Linstead[7] who sought unsuccessfully to dehydrogenate bicyclo[3.3.0.]-öctane over both platinum and selenium. In their attempts to prepare the compound, they noted several interesting differences between the bicycloöctane ring system and the decalin ring system, notably: (a) trans bicycloöctane has a higher heat of combustion than the cis isomer, while in the decalin series the reverse is true; (b) the cis bicyclo compound is unchanged by a platinum catalyst which converts cis decalin into naphthalene; and (c) cis bicycloöctane upon standing over aluminum chloride rearranges to bicyclo[3.2.1]öctane (II)-- a change from a strain-free to a strained configuration--whereas cis decalin under the same conditions is converted irreversibly to the trans configuration-- a change from a strained to a strain-free configuration.



I

II

Blood and Linstead have recently reported a new attempt to synthesize pentalene according to the equations shown below[8].

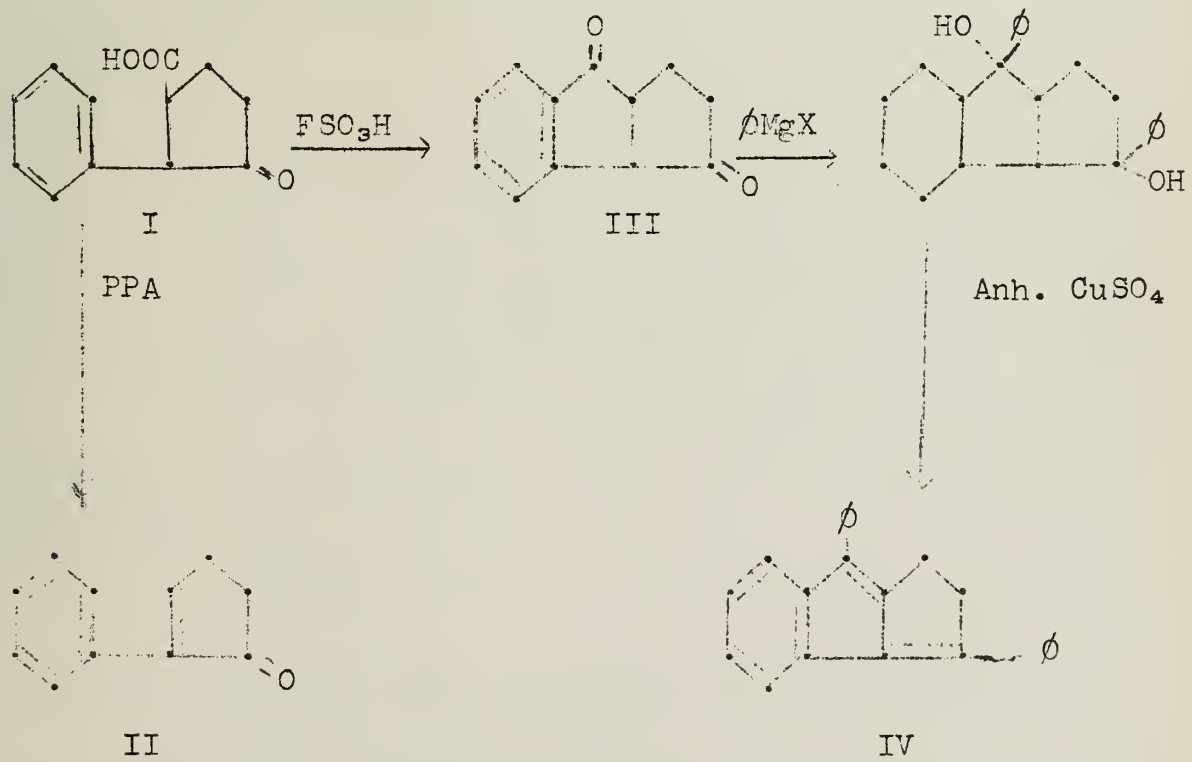


Attempts to decompose (IV) thermally led to the formation of hydrogen bromide and an unsaturated product which at once polymerized to a dark non-volatile material. Treatment of (IV) with silver acetate produced an unsaturated ketonic oil which was so unstable that further investigation of it was abandoned.

It was thought that perhaps (V) could be disproportionated and then dehydrogenated to 1,4-dimethylpentalene. Accordingly, a series of reactions was carried out under increasingly severe conditions, but they all failed to produce any change in the starting material.

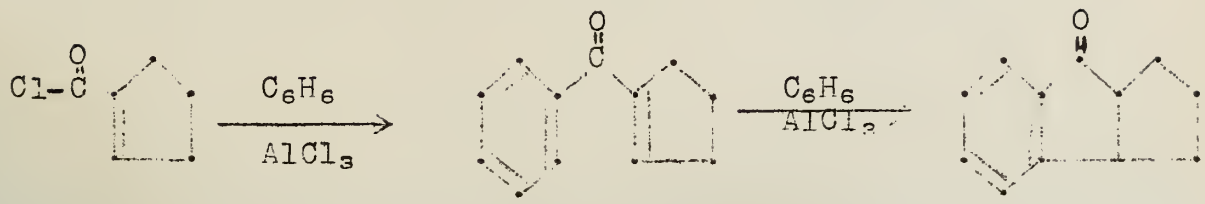
B. Benzopentalene Derivatives: Benzopentalene, 1,2,3,8,9,10-hexahydrocyclopentaindene is not yet known, although its isomer biphenylene has been synthesized[21]. It was thought for a time that biphenylene might actually be benzopentalene. Baker and his collaborators have attempted the synthesis of benzopentalene by the following routes[3,4,6].

(A)



It will be noted that attempted ring closure of 2-phenyl-3-ketocyclopentane-1-carboxylic acid (I) with polyphosphoric acid, a new cyclodehydrating agent which was discovered in this laboratory as being useful in such ring closures[24], failed to give the desired diketone (III). Instead, the elements of formic acid were lost giving rise to 2-phenylcyclopentene-2-one-1. The desired ring closure was accomplished by the use of fluorosulfonic acid, another new cyclodehydrating agent[5].

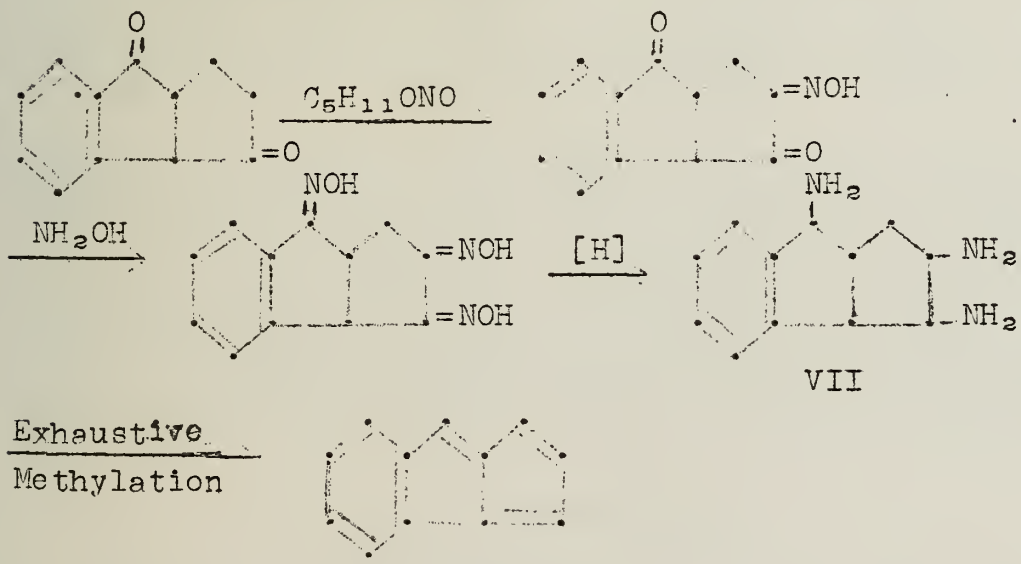
Compound IV could not be further dehydrogenated.



V

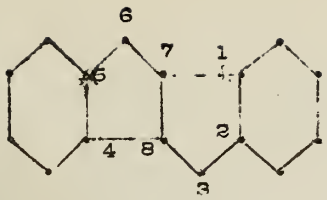
Clemmenson reduction of (V) yielded 1,2,3,8,9,10-hexahydrocyclopentaindene which could not be dehydrogenated catalytically in either the liquid or vapor phase. Bromination of (V) gave and α -bromoketone which was stable toward silver oxide, potassium acetate and pyridine at 120° or toward quinoline at 170°, but was reconverted to (V) by alcoholic potassium hydroxide.

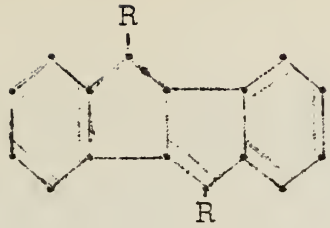
A proposed new synthesis of benzopentalene is shown below[6].



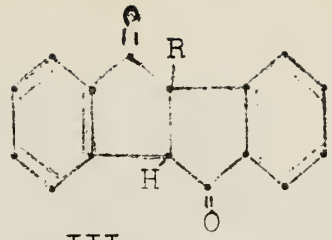
Steps from (VII) have not yet been fully investigated.

C. Dibenzopentalene Derivatives: Dibenzopentalene (I) is the only pentalene to have been synthesized. Its precursor, 3,6-diketodibenzopentalene was prepared by Roser[23] in 1888. Brand and his co-workers have reported the synthesis of several more or less complex dibenzopentalene derivatives of the general types shown below, (II) and (III)[10-16].





II
R = Cl or Ar



III
R = X or Ar.

Treatment of (II) (R = Cl) with zinc dust and acetic acid yielded 2,6-dihydrodibenzopentalene[15,26]. This compound adds bromine but rapidly loses hydrogen bromide and polymerizes, unles some device is employed to remove the HBr as it is formed. By carrying out the reaction in the presence of ammonia, Blood and Linstead[9] were able to isolate dibenzopentalene in 60% of the theoretical amount.

Dibenzopentalene is reported as crystalizing in bronze leaflets which dissolve to give orange-colored solutions. The compound shows plum-colored fluorescence under ultraviolet light. It has no definite melting point, but softens between 275-280°, and chars at higher temperatures. It is insoluble in orthophosphoric acid, but dissolves in concentrated sulfuric acid to give a green solution the color of which is destroyed by addition of ice water. It polymerizes in the presence of traces of mineral acids. Chemical reduction leads to 1,4-addition of hydrogen.

Summary: "The general chemistry of dibenzopentalene is clearly that of a conjugated diene. There is, as yet, no chemical evidence either from formation or reaction that the pentalene system has any special stability, certainly nothing which can be dignified by the term 'aromatic'. Nevertheless, the long-wave absorption, at about 400-420 mμ, of dibenzopentalene and its dichloro-derivative shows a significant difference from that of linear dienes with the same number of pi electrons and indicates some degree of resonance interaction in the excited state of the molecule[9]."

BIBLIOGRAPHY

1. Armit, J. W. and Robinson, R., J. Chem. Soc. 121, 828 (1922).
2. Baker, W., ibid., 1945, 258.
3. Baker, W. and Leeds, W. G., ibid., 1948, 974.
4. Baker, W., and Jones, P. G., ibid., 1951, 787.
5. Baker, W., Coates, G. E. and Glocking, F. ibid., 1951, 1376.
6. Baker, W., Glocking, F. and McOmie, J. F. W., ibid., 1951, 335'
7. Barrett, L. W. and Linstead, R. P. ibid., 1936, 611.
8. Blood, C. T. and Linstead, R. P., ibid., 1952, 2255.
9. Blood, C. T. and Linstead, R. P., ibid., 1952, 2263.
10. Brand, K., Ber. 45, 3071 (1912).
11. Brand, K., and Ludwig, H., ibid., 53, 809 (1920).
12. Brand, K. and Hofmann, F. W., ibid., 53, 815 (1920).
13. Brand, K. and Nuller, K. O. ibid., 55, 601 (1922).
14. Brand, K., and Ott, H., ibid., 69, 2514 (1936).

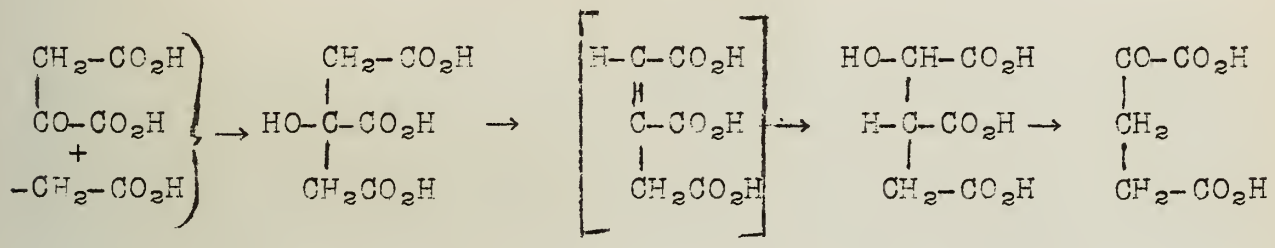
15. Brand, K., and Ott, H., ibid. 69, 2504 (1936).
16. Brand, K., and Hemming, W., ibid., 81, 382 (1948).
17. Brown, R. D., Trans. Faraday Soc. 45, 296 (1949).
18. Brown, R. D., ibid., 46, 146 (1949).
19. Craig, D. P. and Maccoll, A., J. Chem. Soc. 1949, 964.
20. Craig, D. P., ibid., 1951, 3175.
21. Lothrup, W. C., J. Am. Chem. Soc. 63, 1187 (1941).
22. Roberts, J. C. and Gorham, W. F. ibid., 74, 2278, (1952).
23. Roser, W., Ann. 247, 129 (1888).
24. Snyder, H. R. and Werber, F. X., J. Am. Chem. Soc., 72, 2963 (1950).
25. Vogel, E., Ber. 85, 25 (1952).
26. Wawzonek, S., J. Am. Chem. Soc., 62, 745 (1940).

ASYMMETRIC CITRIC ACID

Reported by: Richard F. Heitmiller October 24, 1952

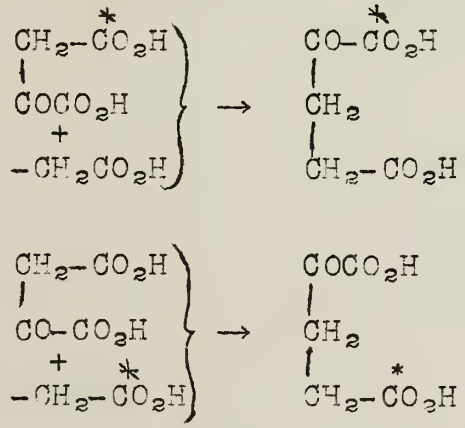
Introduction:

Citric acid is constantly being formed by the condensation of oxalacetic acid and complexed acetate in one stage of the reaction sequence whereby fats and carbohydrates are completely oxidized in all living cells. Once the citric acid is formed, it is converted by the enzyme aconitase to isocitric acid which in turn is oxidize to α-ketoglutaric acid. This complete reaction sequence is shown below.[1]



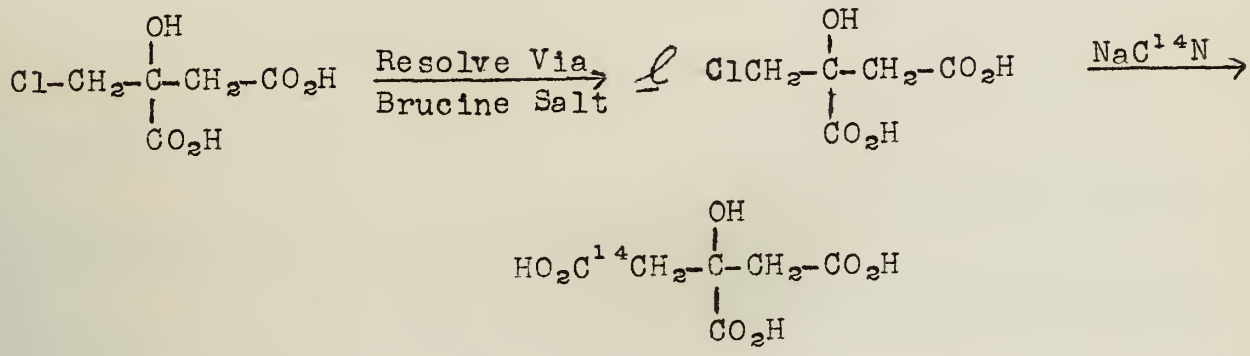
Specificity of Enzyme Attack:

It has been observed in many laboratories that when α-C^{14}-carboxyl labled oxalacetic acid is used, the α-ketoglutaric acid formed from the above sequence of reactions contains virtually all of the C^{14} in the carboxyl group next to the carbonyl group in α-ketoglutaric acid.[2] If, however, C^{14}-carboxyl labled acetic acid is used, virtually all of the C^{14} is found in the carboxyl group more remote from the carbonyl group in α-ketoglutaric acid.[3,4] Similar experiments were carried out with C^{11} and C^{13} with analogous results, these are summarized below:[5,6]

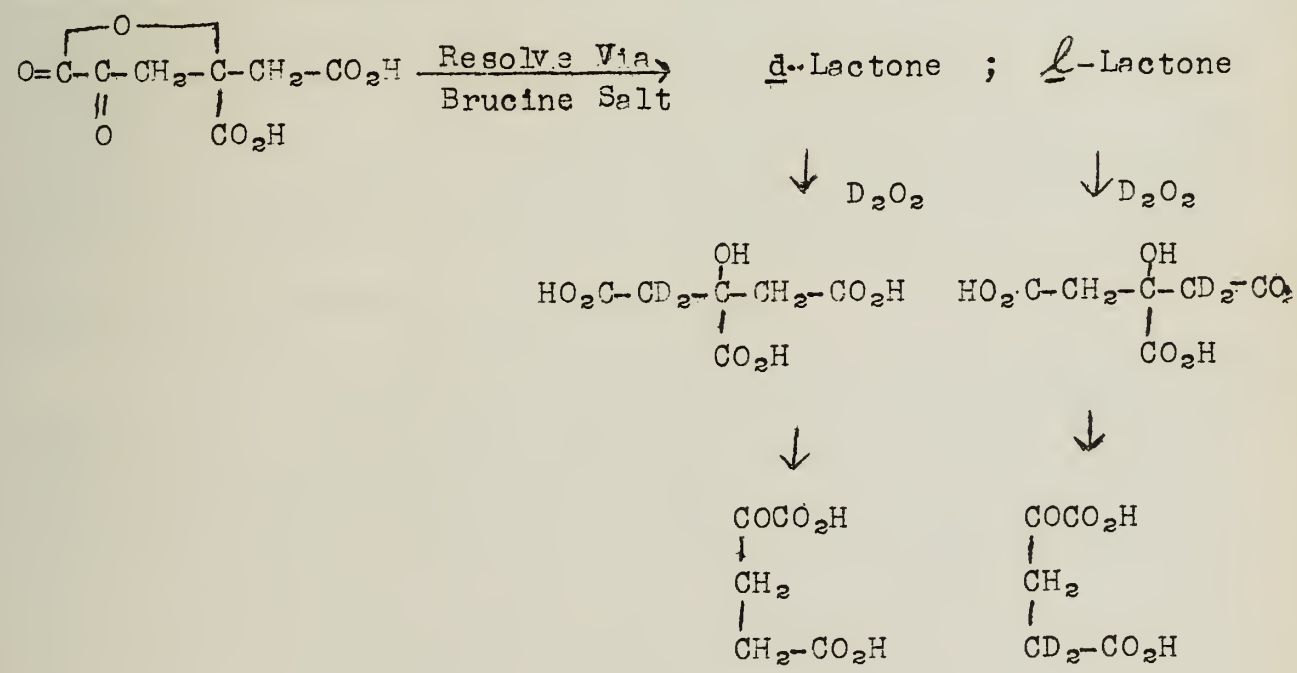


A C^{14} carboxyl labled citric acid has been isolated by Wilcox,

Heidelberger and Potter by the following series of reactions.[7]



The apparent difference in reactivity of the two $-CH_2CO_2H$ groups in citric acid has been demonstrated even more completely by Martius and Schorre who synthesized α,α-dideuterocitric acid and resolved each of the isomers. The levo isomer was converted to α-ketoglutaric acid which contained nearly all the deuterium, and the dextro isomer was converted to α-ketoglutaric acid which contained no deuterium. This reaction sequence is shown below.[8,9]



Asymmetric Citric Acid:

A theoretical explanation for the conversion of a compound C(AABD) where one of the like groups is isotopically labled, to a product in which the isotope is asymmetrically distributed has been presented by Ogsten.[10] His theory is based on a pair of assumptions which are mutually dependent, they are,

1. Both like groups of the molecule must each be complexed with a separate reaction center on the enzyme surface which

contains three active centers.

2. The two combining sites of the like groups must be "catalytically different"

Wilcox, Heidelberger and Potter have modified Ogsten's hypotheses as follows:[7]

1. There must be three distinct and specific points of interaction between enzyme and substrate.

2. Some other condition (steric hindrance, directed forces, or fourth point of interaction).

A much simpler approach to the problem can be made by focusing attention on the interaction between the enzyme and the two unlike groups on the central carbon of the citric acid (the carboxyl and the hydroxyl). These two functions are both reactive but reactive toward different types of reaction centers, they would, therefore, tend to interact non-interchangeably with different centers on the enzyme surface. This would serve to fix the relative orientation of the citric acid molecule with respect to the enzyme. Since the enzyme surface is highly asymmetric, the two like groups will, most probably, lie on areas of the enzyme which differ greatly in their ability in extracting a methylene hydrogen from the $-CH_2CO_2H$. Thus, the reactivity of one of the $-CH_2CO_2H$ groups, i.e. the specificity of the enzyme, is a direct function of its special orientation with respect to the unlike groups as opposed to the dissimilar entantiamorphic orientation to these functions of the similar $-CH_2CO_2H$ groups.[11]

<u>The Asymmetric Synthesis of Citric Acid</u>:

In order to account for its subsequent asymmetric degradation an asymmetric addition must be postulated in the biosynthesis of citric acid. In oxalacetic acid, each of the ketonic carbonyl bonds is diametrically opposite the other. If we consider the two unlike groups in this ketone to be interacting non-interchangeably with the two active sites on the enzyme surface, then one of the ketonic carbonyl bonds will be oriented toward the enzyme surface, and the other away from it; hence the two bonds will differ in their chemical environment, and it would be expected for them to differ in reactivity toward a carbonyl reagent. Thus, in the biosynthesis of citric acid, if only one of the bonds of the ketonic carbonyl in oxalacetic acid is available for reaction with complexed acetate the formation of asymmetric citric acid is explained.

BIBLIOGRAPHY

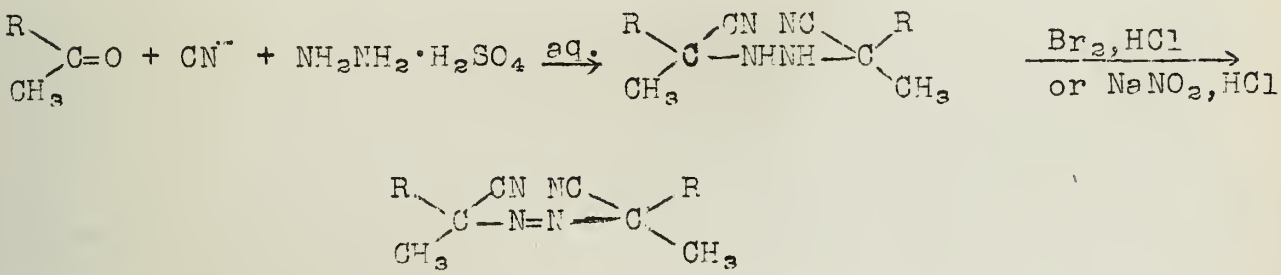
1. H. A. Krebs, Advances in Enzmology, 3, 191 (1943).
2. V. Lorber, M. F. Rudney, and M. J. Cook, J. Biol. Chem., 185, 689 (1950).
3. A. B. Pardee, C. Heidelberger, and V. R. Potter, ibid, 186, 625 (1950).
4. R. G. Gould, A. B. Hastings, C. B. Afinson, I. N. Rosenberg, A. K. Solomon, and Y. J. Topper, ibid, 177, 727, (1949).
5. E. A. Evans Jr., and L. J. Slotin, ibid, 136, 301 (1940).
6. H. G. Wood, C. H. Werkman, A. Hemingway, and A.O. Neir, ibid, 142, 31 (1942).
7. P. H. Wilcox, C. Heidelberger, and V. R. Potter, J. Am. Chem. Soc., 72, 5019 (1950).
8. C. Martius, and G. Schorre, Ann., 570, 143 (1950).
9. C. Martius, and G. Schorre, Z. Naturforsch, 56, 170 (1950).
10. A. G. Ogsten, Nature, 162, 693 (1948).
11. P. Schwartz, Thesis, University of Illinois (1952).

AZO NITRILES

Reported by Barbara H. Weil October 24, 1952

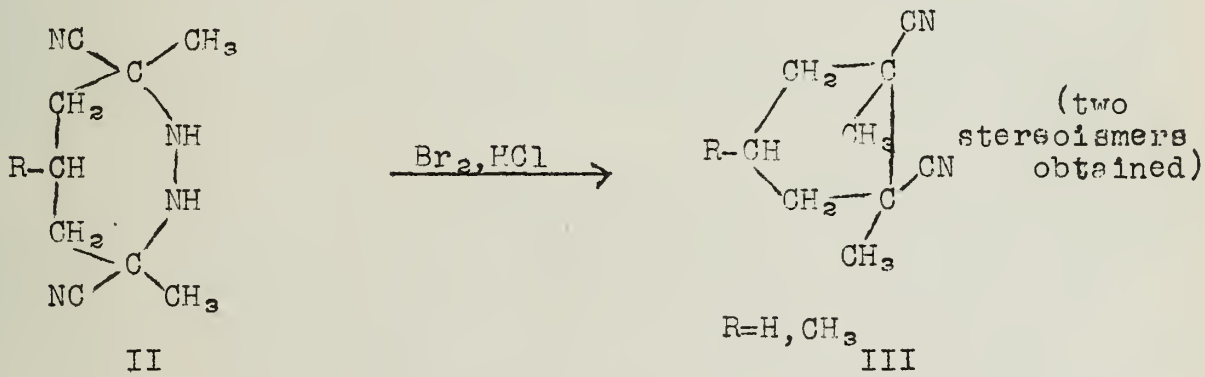
The earliest work on azo nitriles was that of Thiele and Heuser.[1] The procedures they worked out have been modified to apply to a large number of azo-bis-alkyl nitriles.[2-16]

The general method of preparation follows:



I

Compounds have been prepared where R=methyl, ethyl, isopropyl, n-propyl, cyclopropyl, n-butyl, isobutyl, benzyl and p-substituted benzyl. Other azo nitriles have been prepared from cyclopentanone and cyclohexanone. The hydrazo derivatives of some diketones have been made of the general formula II,[10] but when attempts were made to oxidize to the azo compounds, only the substituted cyclobutane or cyclopentane was isolated. (III)



An alternative method of preparation is one described in a recent patent.[11] The ketone is heated with hydrazine hydrate for several hours to prepare the azine which is separated and distilled then heated under pressure with hydrogen cyanide.

One of the properties of azo nitriles which have made them of importance today is their ready decomposition to produce nitrogen and free radicals. Some of them have been found to be quite valuable as polymerization initiators.[6,7,8,9,13,14] The decomposition of the azo nitriles is a convenient synthetic method for

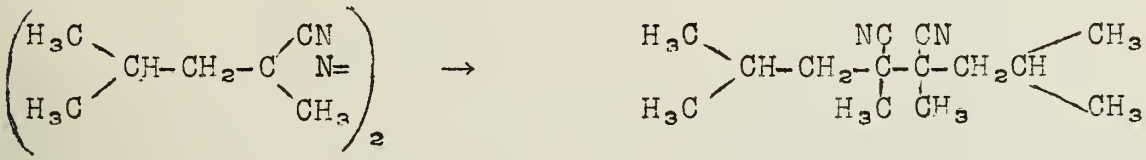
obtaining tetrasubstituted succinonitriles and succinic acids.[1,3,4,6]

Kinetic measurements have been made by several workers[6-10,15] using different methods. The results obtained by all the workers agree substantially: namely, the decomposition reactions of the various azo nitriles appear to be strictly first order and the rate constant is nearly independent of solvent type. The facts that the products of the decomposition of these compounds are tetraalkylsuccinonitriles, that the decomposition rate is little affected by change of solvent polarity and that these compounds initiate vinyl polymerization support the postulate of a primary dissociation into free radicals. The final products in solution depend on the manner and extent of reaction between the primary radical and the solvent. From studies on vinyl polymerization, with radioactive aliphatic azo nitriles as initiators,[12,13] it has been concluded that both types of radicals A• and A-N=N• are formed in the decomposition and are capable of initiating polymerization.

Rate constants have been determined at various temperatures for compounds of the general formula $R\{CH_3\}(CN)-C-N=)_2$. The rate constants are about the same for R=methyl, ethyl, n-propyl, isopropyl and n-butyl, but when R=isobutyl, there is a fivefold augmentation of rate. When the azo compound from cyclohexanone was used, there was a twenty-fold diminution of rate as compared with the main group. There does not appear to be any plausible reason for these major differences on the basis of reasonance due to hyperconjugation or inductive effects. Overberger has studied the group of azo nitriles where R=benzyl, p-chlorobenzyl and p-nitrobenzyl. He found that there is little or no effect of the group in the para position of the benzene ring on the rate of decomposition. He also showed that the steric effect of the benzyl group is comparable to that of the methyl group in AIBN.

A study of Fisher-Hirschfelder models suggests a steric effec for the different rates of decomposition. These models indicate that only the trans-configuration of the azo compound is possible. Little difference in rates of decomposition is observed with different stereoisomers of the azo nitriles. However, there is considerable interference of pairs of groups, R and methyl, at the two ends of the molecule with each other. The interference is of comparable magnitude for compounds whose rates of decomposition fall in the main group; it is considerably more serious for the isobutyl compound and much less so for the cyclohexyl derivative as compared with the others. In the construction of the isobutyl compound, it is impossible to arrange the R and methyl groups in a way which avoids contact of alkyl groups across the C-N=N-C linkage. The repulsive forces arising from this crowding of groups may be expected to strain the C-N bond, displacing its potential surface and decreasing its energy of association. The parallelism between rates of decomposition and degree of strain revealed by the models is striking.

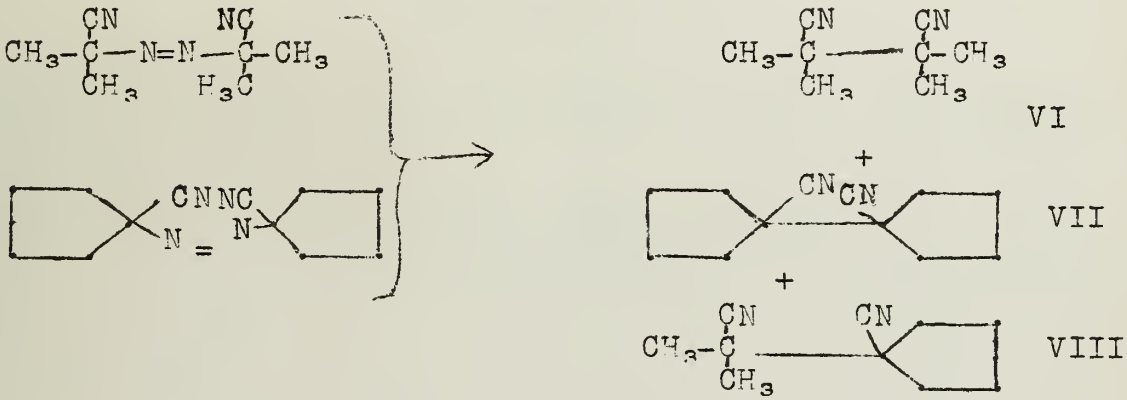
Overberger has investigated extensively the products of decomposition of various azo nitriles.[8-10] Some of the compounds he identified are as follows:



IV
<u>dl</u> or <u>meso</u>

V
(same product in both cases)

No products from the addition of the tertiary radical to the disproportionated products $(CH_3)_2$-CH-CH=C CH_3)(CN) or $(CH_3)_2CH$-CH_2 C(CN)(=CH_2) followed by abstraction of a hydrogen atom by the adduct were found.



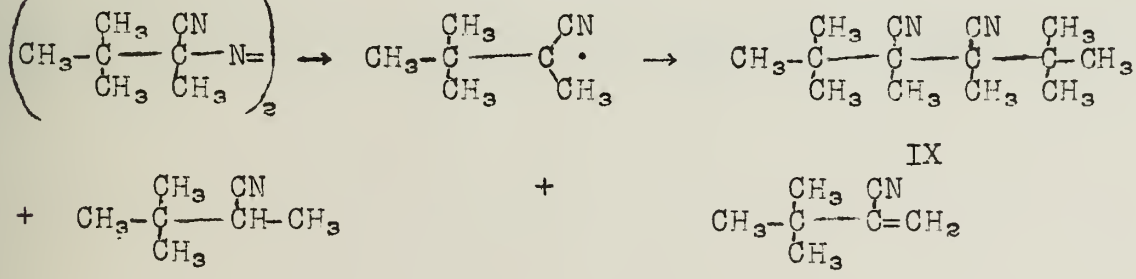
VI

VII

VIII

The isolation of a mixed coupled product (VIII) is indicative of a decomposition mechanism by which relatively free radicals are produced.

The diastereomeric 2,2'-azo-bis-2,3,3-trimethylbutyronitrile was allowed to decompose in benzene solution for three days. Products identified by analysis, reactions and unequivocal syntheses by other methods were the following:

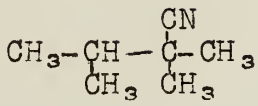


IX

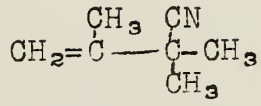
X

XI

No evidence of rearranged products XII and XIII were obtained



XII



XIII

Work now in progress by Overberger[17] involves a study of azo nitriles from cyclic ketones from C=5 to C=10. The rate of decomposition is an accurate measure of differences in ring strain. The results of this investigation have not yet been published.

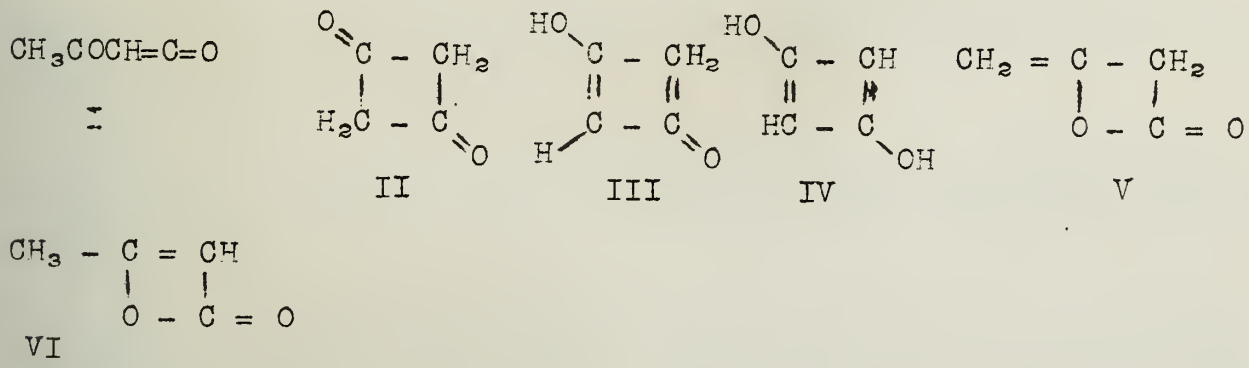
Bibliography

1. J. Thiele and K. Heuser, Ann., 290, 1 (1896).
2. Steff, Diss. Techn. Hochsch. München (1914) 6; Beilstein IV (1st Sup.), 565.
3. A. W. Dox, J. Am. Chem. Soc., 47, 1471 (1925).
4. H. Hartman, Rec. Trav. Chim., 46, 150 (1927).
5. F. M. Lewis, M. S. Matheson, J. Am. Chem. Soc., 71, 747 (1949).
6. C. G. Overberger, M. T. O'Shaughnessy and H. Shalit, ibid., 71, 2661 (1949).
7. C. G. Overberger, P. Fram and T. Alfrey, Jr., J. Polymer Sci., 6, 539 (1951).
8. C. G. Overberger and M. B. Berenbaum, J. Am. Chem. Soc., 73, 2618, 4883 (1951); 74, 3293 (1952).
9. C. G. Overberger and H. Biletch, ibid., 4880 (1951).
10. C. G. Overberger, T. B. Gibb, Jr., S. Chibnik, Pac-tung Huang and J. J. Monagle, ibid., 74, 3290 (1952).
11. W. L. Alderson and J. A. Robertson, 2,469,358, May 10, 1949.
12. L. M Arnett, J. Am. Chem. Soc., 74, 2027 (1952).
13. L. M. Arnett and J. H. Peterson, ibid., 74, 2031 (1952).
14. M. Hunt, P 2,471,959, May 31, 1949.
15. C. E. H. Bawn and S. F. Mellish, Trans. Faraday Soc., 47, 1216 (1951).
16. K. Ziegler, W. Deparade and W. Meye, Ann., 567, 141 (1950).
17. C. G. Overberger et al, Abs. 122nd Meeting, ACS, 53M (Sept., 1952).

THE STRUCTURE OF KETENE DIMER

Reported by W. S. Anderson October 31, 1952

Although diketene has been known for many years, the problem of its structure has never been completely solved. A total of six formulas (I-VI) have been suggested for it since its isolation in 1908 by Chick and Wilsmore as a lachrymatory liquid, b.p. 127°.

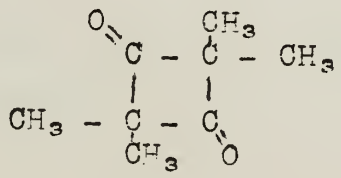


Mixtures and resonance hybrids of certain pairs of these molecules have also been postulated in an attempt to explain its behavior. The substance is widely used both in industry and in the laboratory, but the structure controversy continues still.

Structure Investigations by Physical Methods

(a) Raman effect. Several workers have compared the Raman shifts of diketene with those of other compounds possibly related to it.[1] A comparison with 2,2,4,4-tetramethyl 1,3-cyclobutanedione rules (VII) out the dione structure (II). Structures III and VI do not explain lines in the double bond region of the spectrum. Vinylaceto-β-lactone (V) or acetylketene (I) could explain this part of the spectrum. Dissolving the sample in 2,2,4-trimethylpentane produces no significant change in the spectrum, a fact which suggests that no rearrangement takes place when the substance is dissolved.

(b) Dipole moment. Diketene has a dipole moment of 3.18 D.[2] The symmetric dione structure is totally incompatible with this value. The dimer of dimethylketene, on the other hand, has zero dipole moment; consequently formula (VII) is assigned to it.



VII

(c) Infra-red absorption. Absorption in the 2 -14 μ range indicates that I is not the structure, since no bands are present

which could be ascribed to C=C=O. The absence of the OH bond-stretching frequency is taken to mean that no enols are present. Five strong bands in the double bond region suggest that diketene may be a mixture, since no single structure among those remaining contains more than two double bonds. The spectrum is probably best explained as that of the lactone mixture (V + VI) or possibly of V alone.[3]

The spectrum of the vapor as measured by Miller and Koch[4] shows considerable change in form when the vapor temperature is varied. These authors attribute the change to shifts in the positi of the equilibrium V $\rightleftarrows$ VI.

(d) Potentiometric and conductometric data. Wassermann's measurements[5] indicate that a proton is dissociated from diketene when in dry acetone solution. Structure V most adequately explains this acidity.

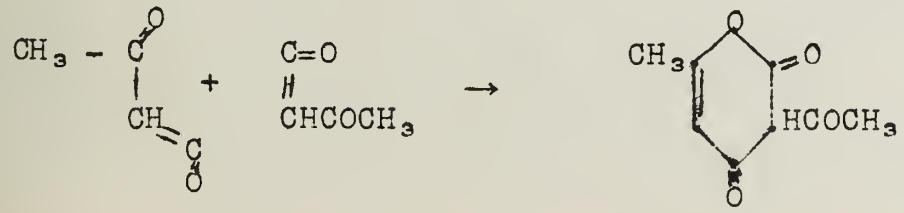
(e) Ultraviolet absorption.[6] By a comparison of the UV absorption of diketene with that of cyclobutanone, the cyclobutanedione structures of diketene are eliminated. The spectrum strongly suggests the presence of the group C=C—C=O. I and VI have this feature; however, the acetyl group of I would be expected to move the absorption of ketene into the visible range to make diketene a colored compound, which diketene is not. Structure VI is left. An approximate calculation of the free energy change for the transformation I $\rightarrow$ VI ($\Delta F \approx -1$ to $-5 \frac{Kcal}{mol}$) indicates that the transformation to acetylketene may be very easy.

(f) Electron diffraction. Workers at Cornell[7] have applied the method of electron diffraction to diketene vapor. They conclude that structures V and VI are compatible with the pattern obtained.

(g) X-ray diffraction. The electron density map and bond lengths determined by this method indicate that V is correct for the crystal molecule.

Structure Investigations by Chemical Methods

(a) The formation of dehydracetic acid, a tetramer of ketene, may be conveniently explained as a Diels-Alder reaction of acetylketene.[9]



(b) The ozonolysis of diketene[10], previously thought to

substantiate the acetylketene structure, has recently been repeated. In the new work no pyruvaldehyde is found in the product; instead, formaldehyde and malonic acid are isolated. These products could be formed from V.

(c) N-bromosuccinimide in chloroform at room temperature brominates in the fashion shown:[11]

$$\text{Diketene} \xrightarrow{NBS} \text{Unstable bromo-derivative} \xrightarrow{C_2H_5OH} \underset{\text{sole product}}{CH_3-\overset{O}{\overset{\|}{C}}-CHBr-COOC_2H_5}$$

If the structure were VI, bromoacetoacetic ester would be the product expected.

(d) Allene and carbon dioxide, previously believed absent in the pyrolysis product, now have been found there.[12] The formation of these products from V is understandable.

(e) Acetoacetylation reactions are explained by the lactone formulas. A new example of this type of transformation is that of a recent patent:[13]

$$\text{polyvinyl alcohol} + \text{diketene} \xrightarrow[\text{1.5 hrs. } 120^\circ]{\text{dry } HCON(CH_3)_2} -CH_2-\underset{\underset{C=O}{|}}{\underset{O}{|}}CH-CH_2-\underset{\underset{OH}{|}}{CH}- \quad \text{19\% of OH groups acetoacetylated}$$

$$-CH_2-\underset{\underset{OH}{|}}{CH}-CH_2-\underset{\underset{OH}{|}}{CH}-$$

$$\underset{\underset{CH_3}{|}}{C=O}$$

References

(1) Taufen and Murray, JACS, 67, 754 (1945).
(2) Angus, Leckie, LeFèvre, LeFèvre, and Wassermann, JCS 1935, 1751.
(3) Whiffen and Thompson, JCS 1946, 1005.
(4) Miller and Koch, JACS 70, 1890 (1948).
(5) Wassermann, JCS, 1948, 1323.
(6) Calvin, Magel, and Hurd, JACS 63, 2174 (1941).
(7) Bauer, Bregnan, and Wrightson, Abstracts of Papers, 109th Meeting of ACS, April, 1946 page 15P.
(8) Katz and Lipscomb, J. Org. Chem. 17, 515 (1952).
(9) Whitmore, Organic Chemistry, 2nd Ed. p. 232.
(10) Hurd and Blanchard, JACS 72, 1461 (1950).
(11) Blomquist and Baldwin, JACS 70, 29 (1948).
(12) Fitzpatrick, JACS 69, 2236 (1947).
(13) Jones, U. S. Patent 2,536,980 [CA 46, 2572 (1952)]

THE SYNTHESIS AND PROPERTIES OF SOME SIMPLE AMINO AND HYDROXY PTERIDINES

Reported by William R. Sherman October 31, 1952

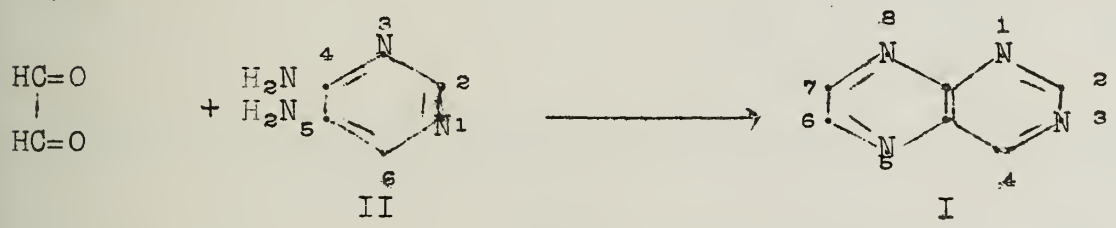
Between 1891 and 1895, Gowland Hopkins[4] isolated several pigments from the wings of butterflies, and reported their extreme infusibility and very slight solubility. At this same time O. Kuhling[5] prepared what is known today as 2,4-dihydroxypteridine, which also exhibited the refractory and insolubility characteristic of Hopkins' compounds. It was not until 1940[8,9] that it was realiz that these two workers had isolated compounds of the same chemical family. Since 1940, the field of pteridine chemistry has drawn an ever increasing number of workers into it, due to the highly important physiological role played by compounds containing the pteridine nucleus.

This paper is limited to a survey of the syntheses and properties of some of the simple mono- and di- amino- and hydroxypteridines. These compounds occur as the nucleus of Hopkins' pigments and of many other naturally occurring compounds, many of which are of extreme biological importance (e.g. xanthopterin, folic acid, rhizopterin, folinic acid, etc.). A great deal of work is now being carried on with simple amino- and hydroxypteridines for the purpose of elucidating their chemical and physical properties, with the hope of throwing light on the role of these substances in animal metabolism.

To this date the apparently anomalous behavior of these simple pteridines toward a variety of reagents is, for the most part, without explanation. Many of these properties seem to be unique to derivatives of this single heterocyclic nucleus.

SYNTHESIS:

The only published synthesis of pteridine (I) itself makes use of the condensation between 4,5-diaminopyrimidine (II) and glyoxal. (1,2)

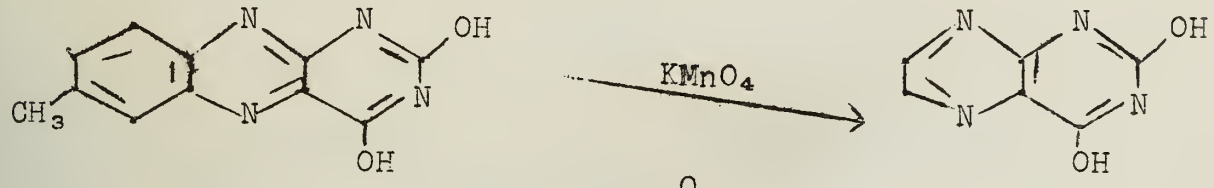


This fundamental reaction is employed in the preparation of the following pteridines:

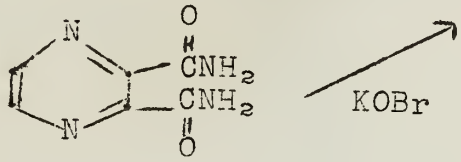
2-hydroxy	(2)	2,4-dihydroxy	(2)
2-amino	(2)	2,4-diamino	(10)
4-hydroxy	(2)	2-amino,4-hydroxy	(10)
4-amino	(2)	2-hydroxy,4-amino	(10)

all of which are prepared by condensing the appropriately substituted 4,5-diaminopyrimidine with glyoxal.

Other routes to 2,4-dihydroxypteridine include Kuhling's original synthesis using tolualloxazine (III)[5], and Gabriel and Sonn's later synthesis from pyrazine-2,3-dicarboxamide (IV).[6]

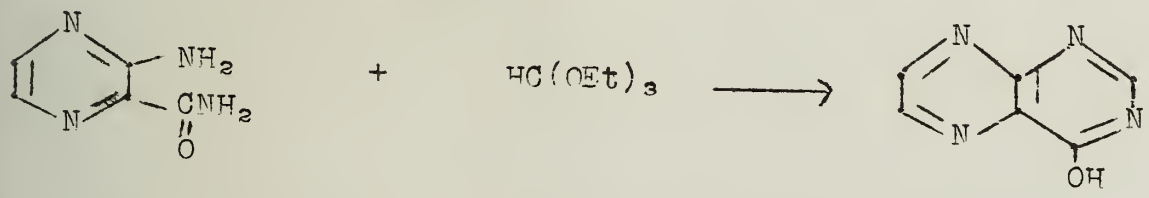


III

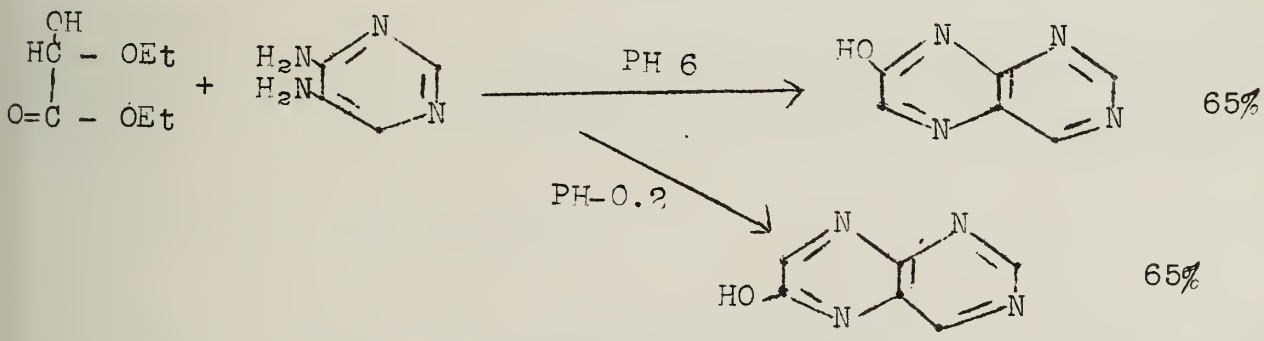


IV

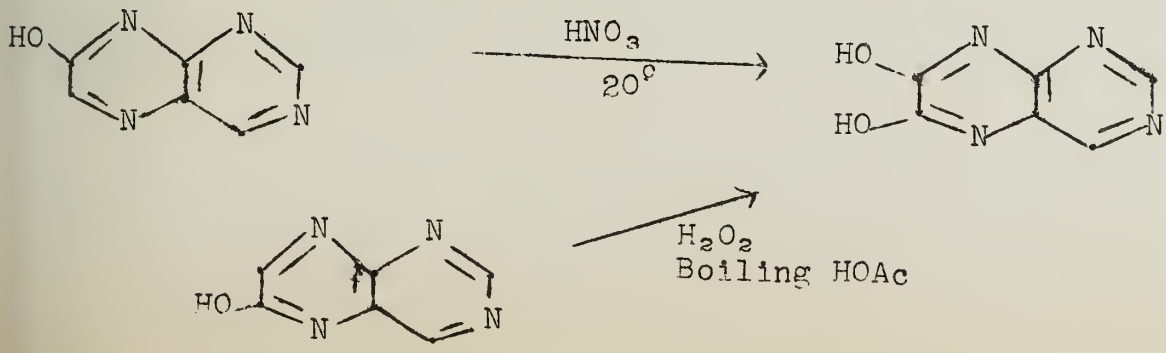
Albert[2] used the following as an alternate route to the 4-hydroxy compound:



In a later paper[7] Albert prepared the two monohydroxypteridines substituted in the pyrazine ring:



The 6,7-dihydroxy compounds may be prepared by the oxidation of either 6- or 7-hydroxypteridine[7].



PHYSICAL PROPERTIES:

Solubility(2):

Introduction of even one hydroxy or primary amino group into the pteridine nucleus greatly lowers solubility in all neutral solvents. A similar effect is observed to a lesser degree in other heteroaromatic bases.

TABLE I
Solubilities in water at 20-25° C (2)

Pteridines	Solubility Ratio	
Pteridine (unsubstituted)	1:7.2	
2-amino-	1:1350	
2-dimethylamino-	1:2.5	
4-amino-	1:1400	
2-hydroxy-	1:600	
4-hydroxy-	1:200	
2-amino-4-hydroxy-	1:57,000	
2-amino-4,6-dihydroxy-	1:40,000	(xanthopterin)
2-amino-4,6,7-trihydroxy-	1:750,000	(leucopterin)

The amino and hydroxy substituents undoubtedly play their more common role as solublizing groups in water; however, the presence of the strongly negative ring nitrogens of neighboring molecules brings powerful hydrogen bonding into play. When a primary amino group is replaced by a dimethylamino group on the pteridine nucleus, the solubility is increased more than five hundred fold (see table I In a similar manner, the hydroxy- and aminopteridines are virtually insoluble in ethanol, benzene or pyridine, while dimethylamino-pteridine is extremely soluble in these solvents.

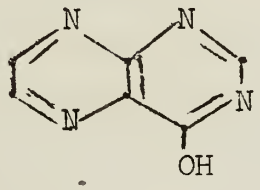
The fact that all known hydroxy- and primary aminopteridines decompose above 240°C., without melting, is another indication of the strengthening these groups give to the crystal lattice. In contrast pteridine and 2-dimethylaminopteridine melt at 140° and 126°C. without decomposition.

Ionizing properties(2):
(see table II)

When a concentrated (colorless) solution of 4-aminopteridine is added to an excess of 0.2N-NaOH, a yellow color appears. Slow hydrolysis to 4-hydroxypteridine takes place under these conditions; however, the ultraviolet absorption spectrum shows the predominant species to be 4-aminopteridine. Thus, 4-aminopteridine forms an anion; this phenomenon has not been observed with the amino quinolines nor with their analogs containing more ring nitrogen atoms.

As would be expected, 4-hydroxypteridine is a stronger acid than the lower order nitrogen heterocycles 4-hydroxyquinoline and 4-hydroxyquinazoline. 2-Hydroxypteridine is a weaker acid than its 4-hydroxy isomeride (no data on the quinoline or quinazoline compounds are available for correlation). The 6- and 7- hydroxy-pteridines are stronger acids than their 2- and 4- isomerides.

The absence of a true hydroxyl function in the four position, and the probable existence of the cyclic amide form, most likely accounts for the lowering of the base strength.



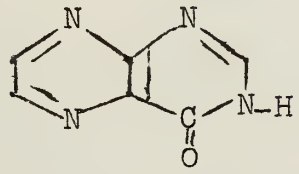


TABLE II
pKa in water at 20°C. (2,7)

Pteridines	Pka, concentration
pteridine (cation)	4.12 M/20
2-aminopteridine (cation)	4.29 M/100
4-amino- (cation)	3.56 M/200
2-dimethylamino- (cation)	3.03 M/100
2-Hydroxy- (anion)	11.13 M/100
4-hydroxy- (anion)	7.89 M/100
6-hydroxy- (anion)	6.7 M/500
6-hydroxy- (anion)	6.41 M/200
6,7-dihydroxy- (mono anion)	6.87 M/500
(di anion)	10.00 M/500
4-hydroxyquinoline	12.4 (in 50% ethanol)
4-hydroxyquinazoline	10.0 (in 50% ethanol)

CHEMICAL PROPERTIES:

Acid and base hydrolysis:

Pteridine, 2-amino- and 2-hydroxypteridine are all destroyed by cold 10N-HCl or boiling N-NaOH. Even absorption on alumina is enough to convert 70% of a 1% benzene solution of pteridine to a red oil of unknown composition[2].

Stability of the pteridine system is increased by substituting in the 4 position. 4-hydroxypteridine is recovered unchanged from a solution of boiling 6N-NaOH. In acid or basic solutions the 4-amino group is smoothly hydrolyzed to a 4-hydroxyl group, with slight concurrent decomposition of the 4-hydroxypteridine in the acid solution.[2]

6-Aminopteridine is hydrolyzed to 6-hydroxypteridine in acid solution. The 6-hydroxy compound is stable in 10N-HCl at 20° and is recrystallized from a hot 15% HCl solution.[7] 7-Hydroxypteridine (the 7-amino compound could not be prepared due to the unstability of the 7-hydroxy compound toward chlorinating and aminating agents) shows a similar behavior but is destroyed by prolonged boiling in N-H_2SO_4. 6-Hydroxypteridine is unstable to base, decomposing to an uncharacterized compound in 0.1N-NaOH. The 7-hydroxy compound is undecomposed by boiling N-NaOH.

TABLE III (14)
Hydrolysis by boiling 6N-HCl

Pteridine	Time	Product
4-hydroxy-2-amino	0.5 hrs.	no reaction
	30 hrs.	2,4-dihydroxypteridine
2-hydroxy-4-amino	0.33hrs.	2,4-dihydroxypteridine

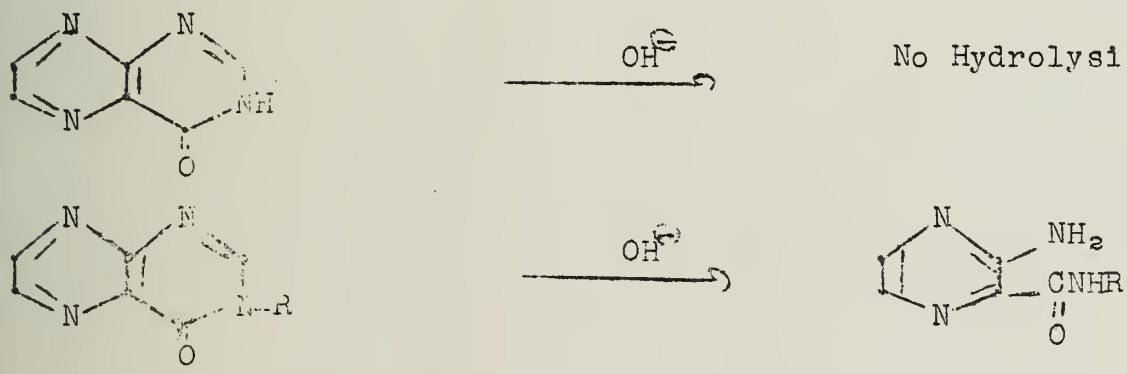
Deamination by HONO

2-hydroxy-4-amino	no reaction
4-hydroxy-2-amino	2,4-dihydroxypteridine

Since mineral acid will hydrolyze an imino group but not an amino group, and the converse is true for nitrous acid, the above information (table III) would indicate that an amino group in the four position exists predominately in the imino rather than in the amino form.

The following consideration might also have some bearing on the difference in the ease of hydrolysis of the amino groups in the 2- and in the 4- positions of pteridine.. An amino group in the 2-position partakes of the guanidine structure, while one in the 4-position is of an amidine type. It is recognized that guanidines are more stable to acid hydrolysis than amidines..

If the base-stable 4-hydroxypteridine is alkylated in the 3-position, it undergoes a profound change in character. As a direct result of the substitution the 3-alkylated, 4-(keto)-pteridine undergoes ring cleavage in 0.1N-KOH[3].



This effect may be due in the first case to the formation of a simple anion which resists further base attack, and in the second case, where no stable anion can be formed, to a hydrolytic attack on C-2, and subsequent ring opening.

BIBLIOGRAPHY

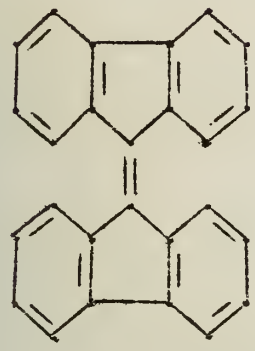
1. W. G. M. Jones, Nature, 162, 524, (1948).
2. A. Albert, D. J. Brown and G. Cheeseman, J. Chem. Soc., 103, 474 (1951).

3. E. C. Taylor, Jr., J. Am. Chem. Soc., 74, 2380, (1952).
4. F. G. Hopkins, Nature, 40, 335, (1889); 45, 197, 581, (1892); Trans., Roy. Soc., B186, 661, (1895).
5. O. Kuhling, Ber., 28, 1968, (1895).
6. S. Gabriel and A. Sonn, Ber., 40, 4857, (1907).
7. A. Albert, D. J. Brown and G. Cheeseman, J. Chem. Soc., 298, 1620, (1952).
8. R. Purrmann, Ann., 544, 162, (1940); 546, 98, (1940).
9. H. Wieland and R. Purrmann, Ibid, 163, (1940).
10. E. C. Taylor, Jr. and C. K. Cain, J. Am. Chem. Soc., 71, 2538, (1949).

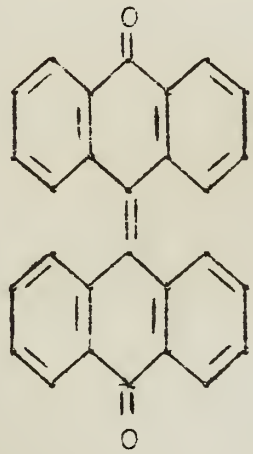
Hydrocarbons with Intercyclic Double Bonds

Reported by M. J. Fletcher November 7, 1952

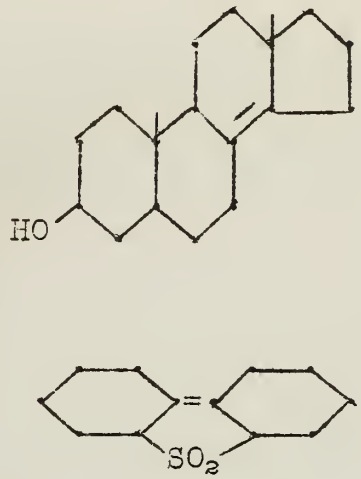
A double bond may be regarded as intercyclic if it lies between two rings, as for example, in the following compounds:



Dibiphenyleneethylene

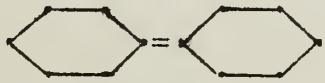


Dianthrone



Bis-cyclohexylidene 2,2'-sulfone

These compounds, however, are special cases; the first two have intercyclic double bonds which are conjugated at both ends with aromatic systems, while in the last two the intercyclic double bonds are also intracyclic. On the other hand, bis-cyclohexylidene itself has an intercyclic double bond with no modifying factors.



I

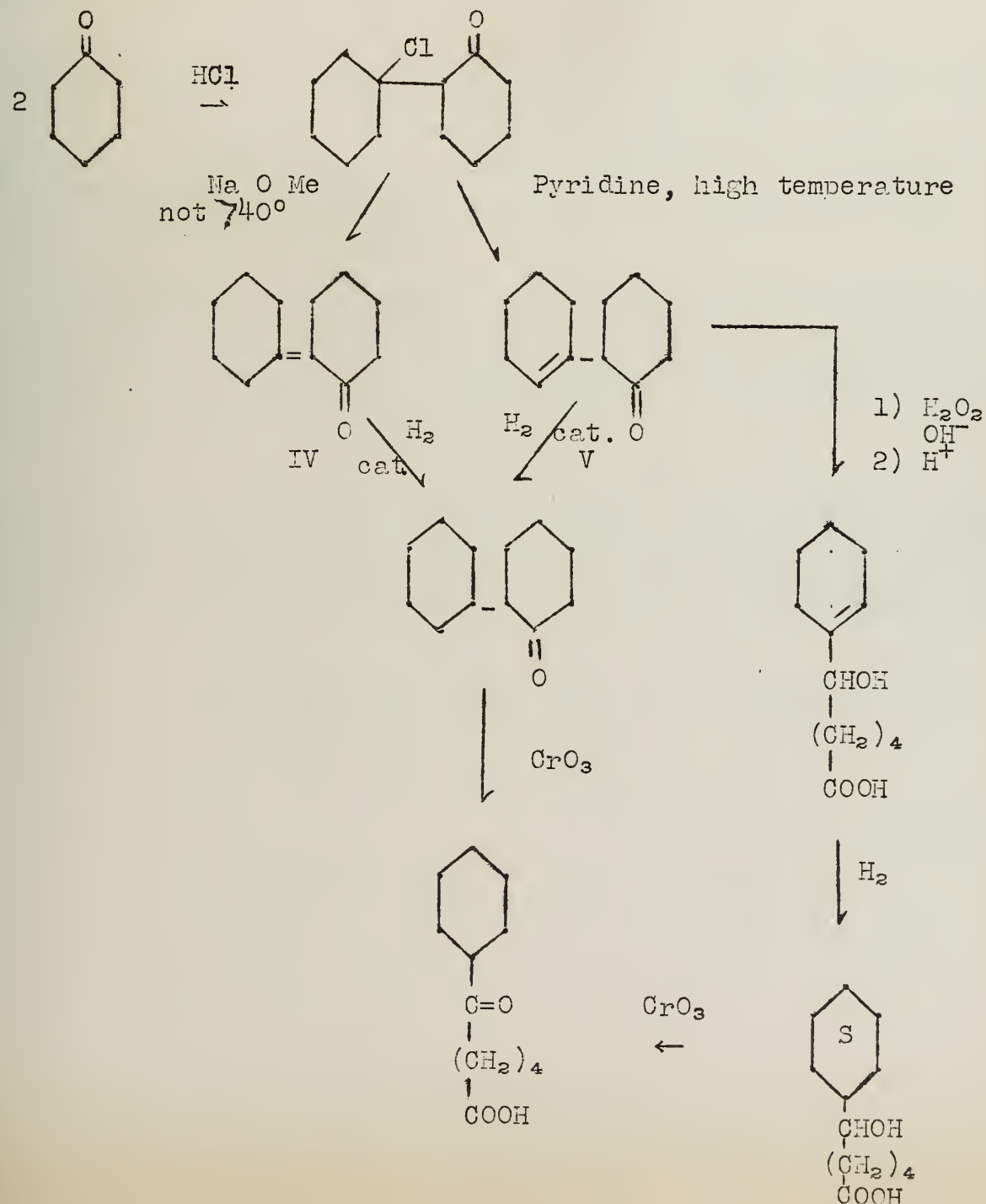
Bis-cyclohexylidene has been reported several times in the literature, but, until it had been prepared by Criegee[1] and coworkers only one accurate description of it was extant, and in this case the compound was not recognized for what it was.

Sabatier and Maihle[2] thought they had obtained I by dehydrating 1-cyclohexylcyclohexanol (II) with zinc chloride, or distilling it over thorium oxide, but later work by Huckel and Neunhoffer[3] showed that it was the isomeric hydrocarbon III.

II III

Senderens and Aboulenc[4] reported that they had obtained I as a byproduct in the dehydration of cyclohexanol with concentrated sulfuric acid at 130°, although they gave no analytical data or structure proof. A consideration of its properties, however, shows it to be dicyclohexyl ether.

Finally, Zelinsky and Schuikin[5] reported that they had prepared I by the Wolff-Fischner reduction of α-cyclohexylidene-cyclohexanone (IV). (IV) has long been assumed to be the product of the alkaline self condensation of cyclohexanone. Reese[6] has shown, however, that this is not the case. The reactions he used to prove this are as follows:



Reese has not proved the structure of IV, but he has proved that this structure is correct for V, which is the ketone obtained by the alkaline self-condensation of cyclohexanone.

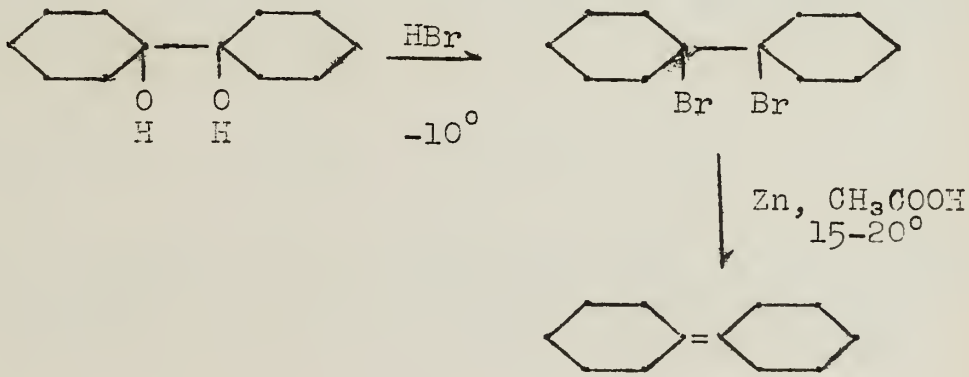
Grundman[7] obtained a very small amount of a hydrocarbon which seems to be I from the vapor phase nitration of cyclohexane. Although he considered the structure I for this compound, he rejected it on the basis of literature information now known to be false.

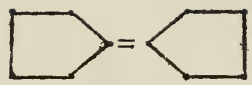
At first Corigee[1] and coworkers attempted to prepare I by dehydration of II under milder conditions than those Sabatier and Maihle had used, but even the Chugaev reaction led to the hydrocarbon III.

Next the action of zinc on the dibromide obtained from cyclohexanone pinacol, to which the structure 1,1'-dibromo-bis-cyclohexyl had been assigned[8], was tried, but this compound turned out to be very stable, not only toward zinc in acetic acid, but also such reagents as magnesium in ether, metallic lithium, and sodium in boiling dioxane, yielding, when it reacted at all, unsaturated bromo compounds. With copper-plated zinc in dioxane, however, a saturated hydrocarbon of unknown structure was obtained.

According to Mereshkowshi's rule[9], ditertiary dibromides, when treated with potassium acetate in acetic acid, lose all their bromine to form dienes, while disecondary and secondary-tertiary dibromides lose only part of their bromine to form unsaturated bromo-compounds. This indicates strongly that the structure assignment to this dibromide is incorrect.

Besides, by the action of hydrobromic acid on cyclohexanone pinacol at -10°C, a dibromide was obtained which was easily converted into I in 85% yield by the action of zinc in acetic acid at 15-20° for 1/2 hour. Similarly, bis-cyclopentylidene (VI) and bis-cyclo-heptylidene (VII) may be prepared in yields of 90% and 85% respective





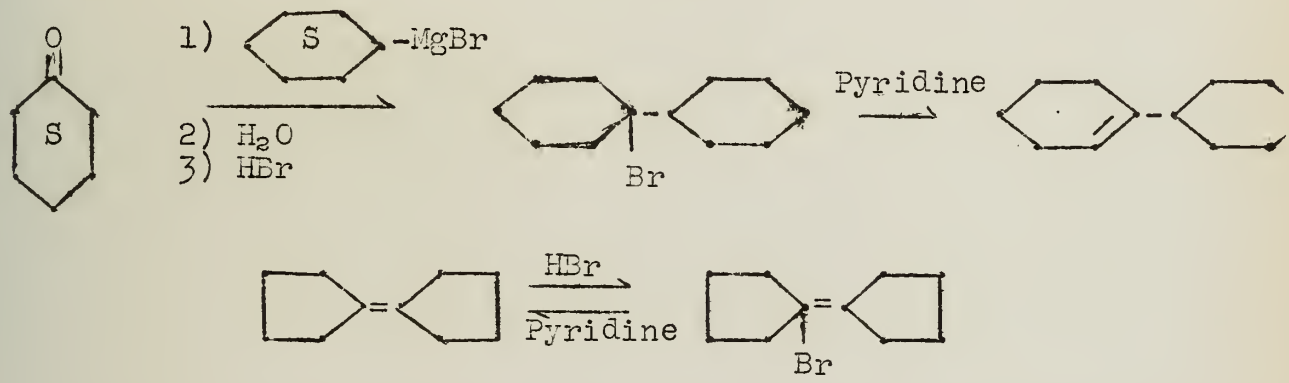
VI

VII

The necessary intermediates for the preparation of the four and eight membered compounds have not yet been obtainable.

The structures of these hydrocarbons were proved by the fact that, on oxidation with osmium tetroxide, they were all reconverted to the corresponding pinacols.

The stability, as well as the ease of formation of these compounds seems to be strongly dependent on the size of the ring. This may be illustrated by the following reactions:



It is of interest to note here that almost all elimination reactions not involving bulky groups, or in which the molecule does not contain a positive charge to start with, as, for example, a tetra-alkylammonium salt, give Saytseff elimination, yielding the most highly branched olefin possible. For instance, diethylisopropyl-chloromethane yields, on treatment with alcoholic potassium hydroxide 1,1-dimethyl-2,2-diethyl ethylene.

$$(CH_3)_2CH-\underset{\underset{Cl}{|}}{C}-(C_2H_5)_2 \xrightarrow[C_2H_5OH]{KOH} (CH_3)_2C=C(C_2H_5)_2$$

However, in all cases where a competing elimination is possible in the attempts to prepare bis-cyclohexilidene, the isomeric hydrocarbon III was obtained. This was not the case with bis-cyclopentylidene. These facts may be explicable on steric grounds.

Bibliography

1. R. Criegee, E. Vogel and H. Herger, Ber., 85, 144 (1952).
2. P. Sabatier and A. Maihle, Compt. rend., 138, 1323 (1903); Cf. ibid., 154, 1392 (1912); Bull. soc. chim., [3], 33, 78 (1905).
3. W. Hückel and O. Neunhöffer, Ann, 477, 106 (1930).
4. B. Senderens and I. Aboulenc, Compt. rend., 183, 831 (1925); 187, 1104 (1927).
5. N. Zelinsky and N. Schuikin, Chem. Journ. Ser. A. Journ. allg. Chem., 64, 671 (1932) [Chem Zentr., 1933, II, 1673].
6. J. Reese, Ber., 75, 384 (1942).
7. Ch. Grundmann, Angen. Chem., 62, 556 (1950).
8. O. Wallach and F. Pauly, Ann, 381, 113 (1911).
9. K. B. Mereshkowski, Ann, 431, 235 (1923).

NEW REACTIONS OF PYRROLES

Reported by Robert E. Putnam November 7, 1952

Introduction

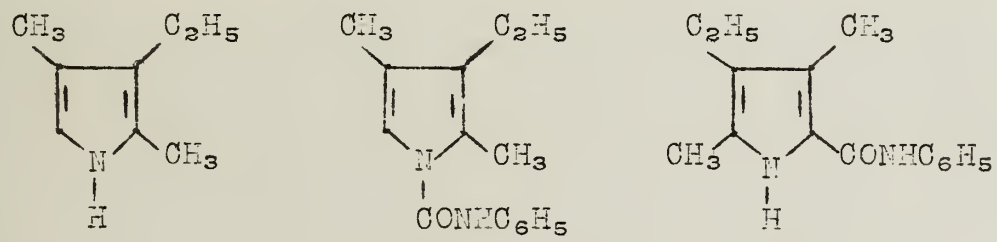
Pyrroles have often been compared to phenols because of their reactivity towards electrophilic substitution. Like phenols they can be nitrated, halogenated, alkylated, acylated and coupled with diazonium salts. In general, substitution takes place at an α-position. However, when both α-positions are blocked substitution at a β-position occurs readily. A different orientation is noted with the potassium salts of pyrrole and its derivatives. These compounds react with such reagents as RX, RCOX, ArCOX and $ClCO_2Et$ to give N-substituted pyrroles. Recently Treibs, Michl and Ott have reported the reactions of pyrrole and alkylpyrroles with benzoyl chloride, isocyanates and diketene. These reactions will be discussed in the present seminar.

Benzoyl Chloride

The most general method of preparation of N-acyl and N-aroyl pyrroles is treatment of the potassium salt of the pyrrole with an acid chloride (1, 2). Pyrrole itself can be converted to an N-acyl pyrrole by heating with the appropriate aliphatic acid anhydride (1). Treibs and Michl have now reported the reaction of pyrroles with benzoyl chloride and p-nitrobenzoyl chloride under the conditions of the Schotten-Baumann reaction to give N-benzoyl derivatives. Pyrroles substituted with negative groups do not react. Pyrrole itself gives an oil while alkylpyrroles give colorless, high melting solids suitable for characterization.

Isocyanates

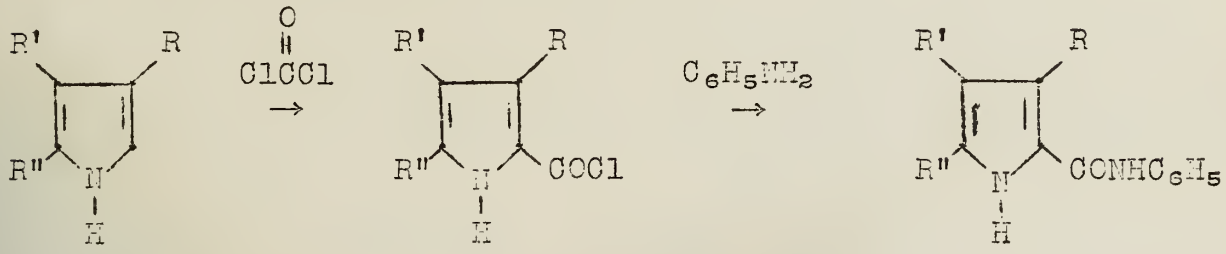
There is only one report in the literature of the reaction of a pyrrole with an isocyanate. Fischer, Süs and Meilguny (4) added phenyl isocyanate to kryptopyrrole, I, and obtained a solid which they formulated as II. Treibs and Ott (5) have shown that this



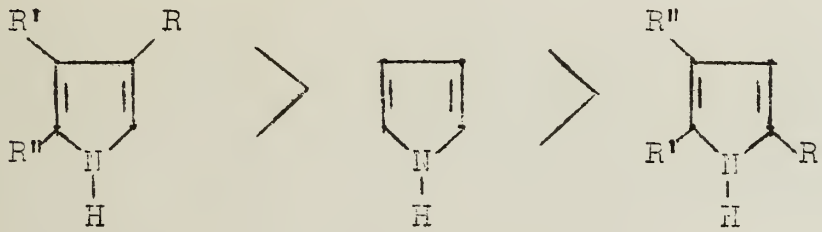
I II III

reaction is quite general for alkylpyrroles but that the products are of type III rather than of type II. The structures were proved by comparison of the products with pyrrolecarboxanilides prepared

by treatment of the pyrrole with phosgene and reaction of the acid chloride formed with aniline. The anilides obtained by the two methods were identical.



The reaction with isocyanates is limited to those pyrroles which do not have electron withdrawing substituents. Compounds such as 2,4-dimethyl-3-carbethoxypyrrole, 2-methyl-3-carbethoxypyrrole and 2,4-diphenylpyrrole fail to react. With pyrrole and alkylpyrroles addition occurs without a catalyst. This is remarkable in view of the fact that carbon alkylation with phenyl isocyanate usually requires a catalyst. Thus phenyl isocyanate attacks benzene in the presence of aluminum chloride to give benzanilide (6) and also attacks active methylene compounds in the presence of alkoxides to give aliphatic anilides (7). The ease of reaction of pyrroles is given by the following sequence where R and R' are alkyl and R" is alkyl or hydrogen. In addition to phenyl isocyanate,

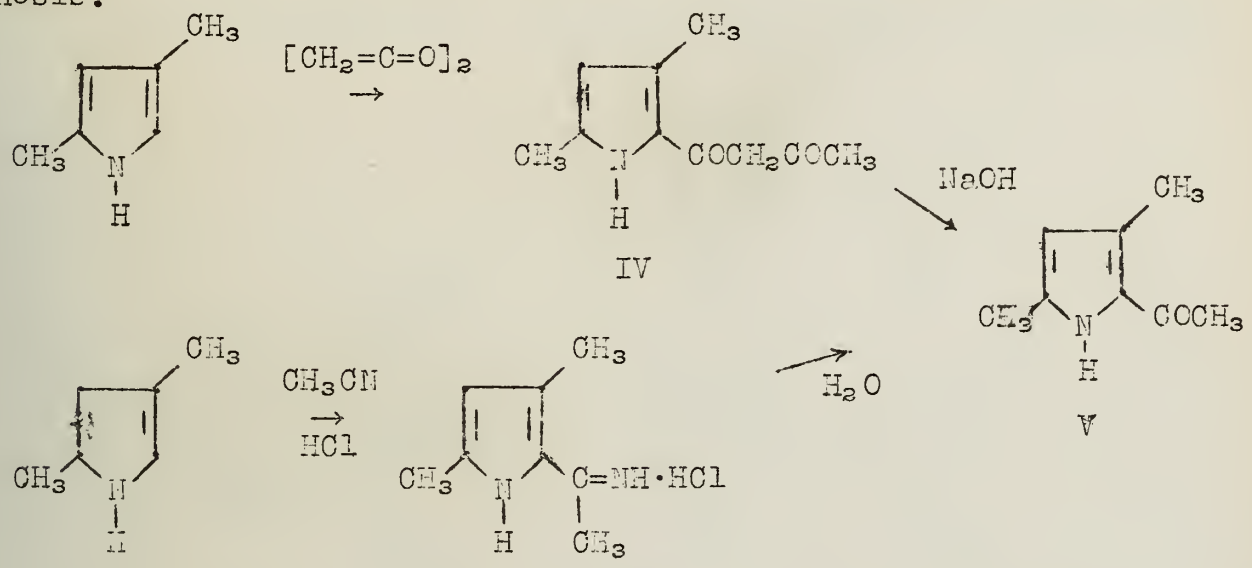


substituted phenyl isocyanates and benzyl isocyanate are satisfactory reactants.

The products are extremely stable, crystalline solids. They are unaffected by long boiling with concentrated hydrochloric acid or concentrated sodium hydroxide. Heating with concentrated sulfuric acid or fusion with potassium hydroxide causes some hydrolysis, the original pyrrole being isolated in each case. The presence of the carboxanilide group deactivates the ring somewhat. Halogenation of the pyrrole nucleus is still possible but introduction of an aldehyde group by the Gattermann method is very difficult. The anilides do not couple with diazonium salts. However, they do condense with formaldehyde yielding dipyrrylmethanes, a reaction typical of most pyrroles.

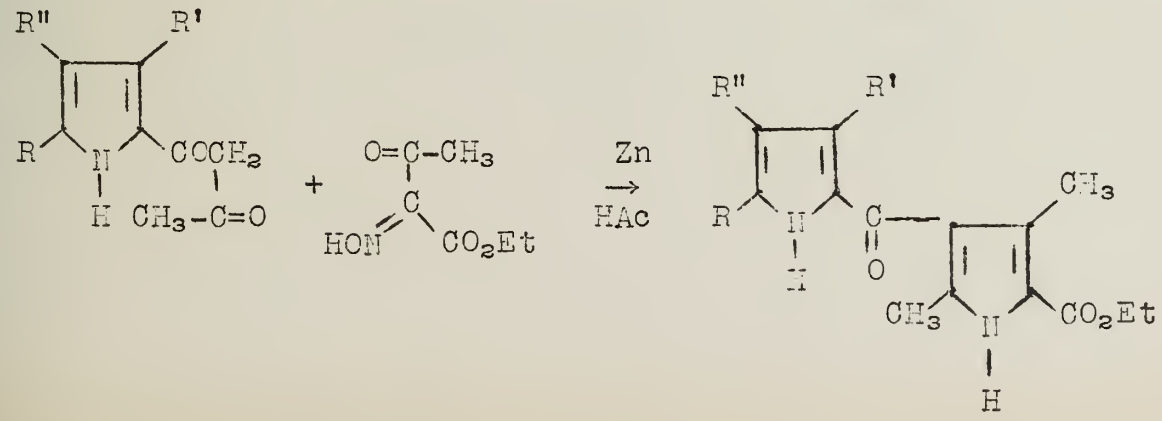
Diketene

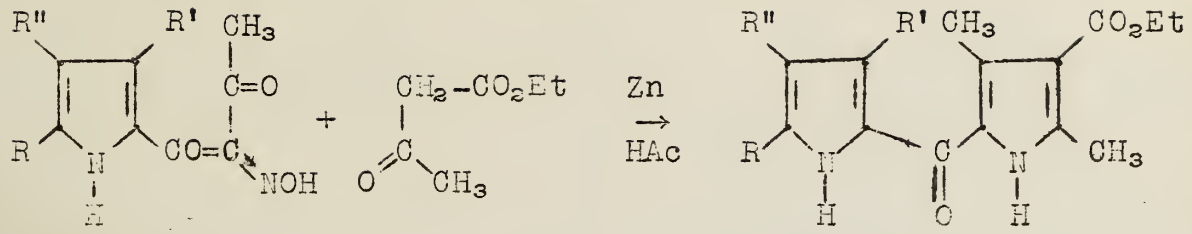
Alkylpyrroles add to diketene in the same way as to isocyanates (8). Again substitution takes place at a nuclear carbon atom. This was shown as follows. The product of the reaction between diketene and 2,4-dimethylpyrrole, IV, was heated with concentrated sodium hydroxide to give 2,4-dimethyl-5-acetylpyrrole, V, which was identical with the known acetylpyrrole prepared by a Houben-Hoesch synthesis.



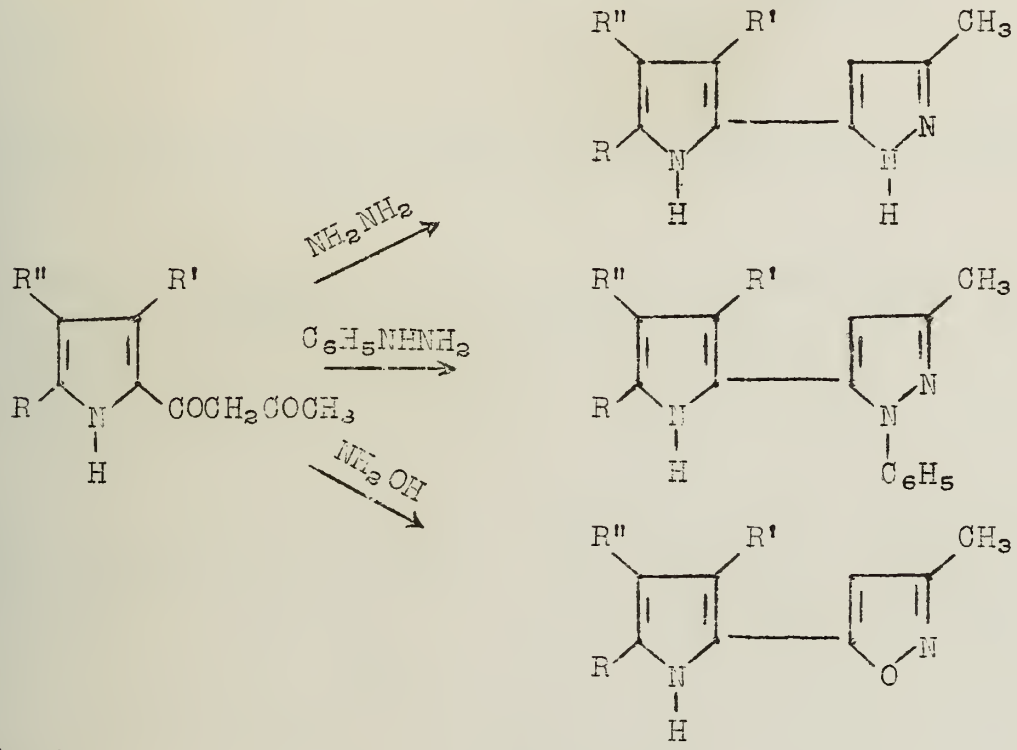
It is notable that the position of an alkyl group on the pyrrole nucleus does not influence the ease of reaction of the pyrrole with diketene. Moreover, the addition to diketene is strongly influenced by catalysts. Sodium acetate and other bases increase the rate of reaction but not the yields, since they also catalyze the polymerization of diketene. As in the case of addition to isocyanates, negatively substituted pyrroles do not react.

The products have proved to be very useful in the synthesis of more complicated heterocycles. Inasmuch as they are β-diketones the Knorr synthesis is applicable to the preparation of dipyrrylketones. By suitable choice of reactants a variety of products may be obtained:



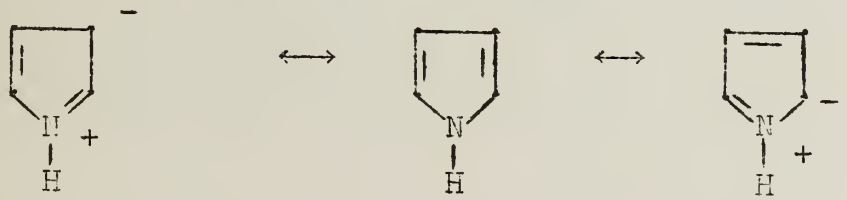


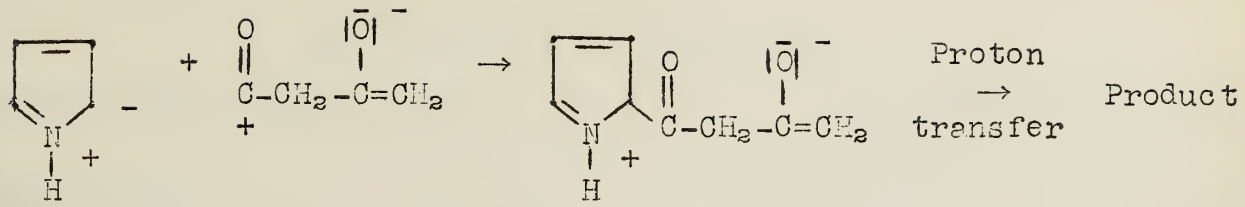
Hydrazine, phenyl hydrazine and hydroxylamine react at room temperature to give, respectively, pyrazylpyrroles and isoxazylpyrroles.

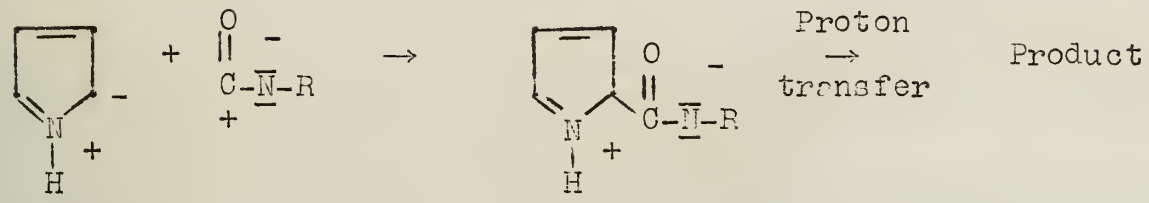


Mechanism

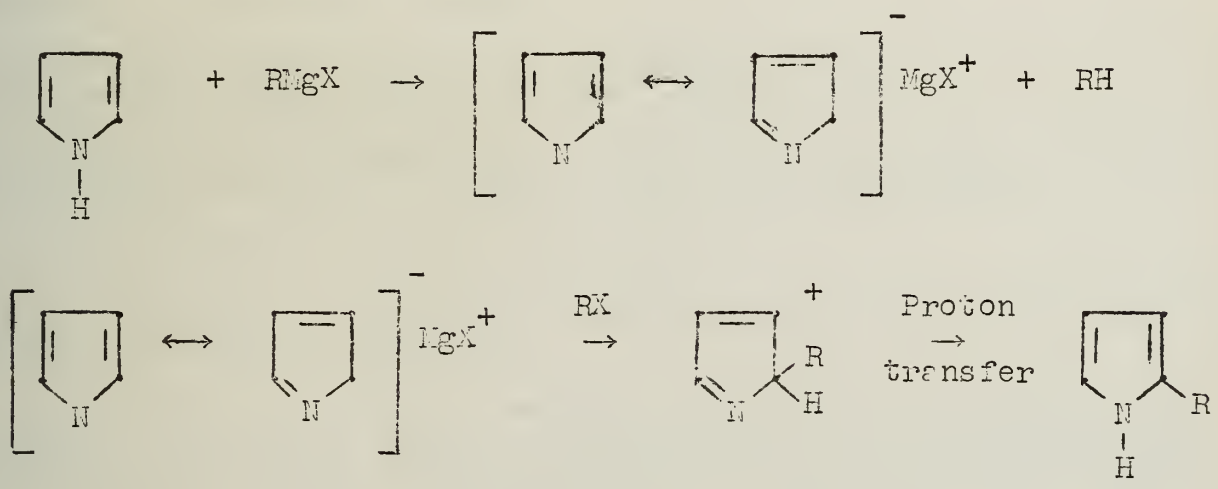
Treibs and Michl (8) explain the reaction of pyrroles with isocyanates and diketene as an attack by the pyrrole on the polarized form of the isocyanate or diketene.







This mechanism is quite similar to that generally accepted for reactions of pyrrole Grignard reagents.



Bibliography

1. Fischer and Orth, "Die Chemie des Pyrrols," Vol. 1, p. 27, 1934.
2. Rainey and Adkins, J. Am. Chem. Soc., 61, 1104 (1939).
3. Treibs and Michl, Ann., 577, 115 (1952).
4. Fischer, Sus and Neilguny, Ann., 481, 159 (1930).
5. Treibs and Ott, Ann., 577, 119 (1952).
6. Leukart, Ber., 18, 873 (1885).
7. Petersen, Ann., 562, 206 (1949).
8. Treibs and Michl, Ann., 577, 129 (1952).

THE SKELETON OF PICROTOXININ

Reported by R. Thomas Stichl November 7, 1952

Introduction

In 1812 a naturally occurring material, picrotoxin, was isolated and found to be physiologically active. Almost seventy years elapsed before attempts were made to elucidate its structure. Investigation revealed that picrotoxin is composed of two substances: picrotoxinin $C_{15}H_{16}O_6$, and picrotin, $C_{15}H_{18}O_7$.

Conroy[1-4] has recently reported structure studies on picrotoxinin and has synthesized dl-picrotoxadiene. He also formulated a skeleton for picrotoxinin and ventured a tenable structure.

Evidence for Assigned Structure

Infrared suggests that picrotoxinin is composed of two five-membered lactone rings (1777 cm.$^{-1}$ and 1798 cm.$^{-1}$).

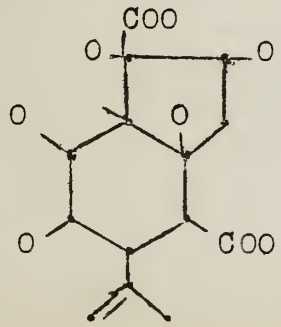
Results of bromination, hydrogenation, ozonolysis, and infrared (weak band at 1657 cm.$^{-1}$) indicate only one double bond.

No carbonyl derivatives are formed.

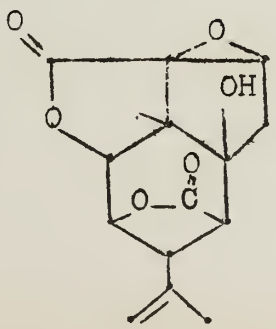
A Zerevitinov determination and infrared (3450 cm.$^{-1}$) show the presence of only one hydroxyl.

Bromination yields two sparingly soluble, stereoisomeric monobromides, $C_{15}H_{15}O_6Br$, which can quantitatively be debrominated by zinc to picrotoxinin. Infrared studies indicate that the monobromo compounds have neither a double bond nor a hydroxyl group. The absence of the latter is further confirmed by a Zerevitinov determination. Thus, both the hydroxyl and the double bond must have been involved in the bromination reaction. This also lends some support to the assumption that the sixth oxygen is linked as an ether and is not present as hydroxyl.

Conroy arrives at a skeletal structure (I); he deduces a complete structure (II) which is to be substantiated in later papers.

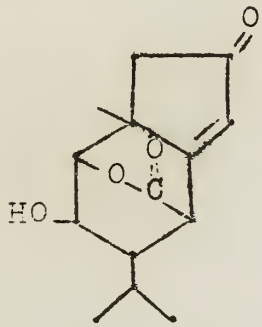


I



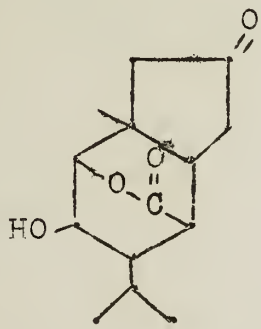
II

Several reactions of picrotoxinin and its derivatives are employed in assigning structure I. Although structures can be written for most of the compounds involved in these reactions, proof of structure has been published only through picrotoxinide (III), which is related to a picrotoxinin derivative and to picrotoxadiene (VIII) through the following transformations.

Dihydro-α-picrotoxininic Acid $\xrightarrow{230^\circ}$  + CO_2 + H_2O

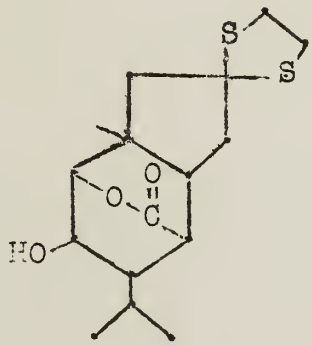
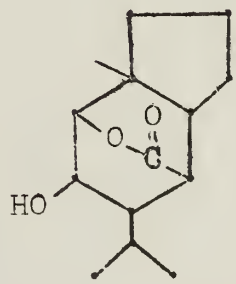
III

Picrotoxinide

III $\xrightarrow[\substack{PtO_2 \\ CH_3OH}]{H_2}$ 

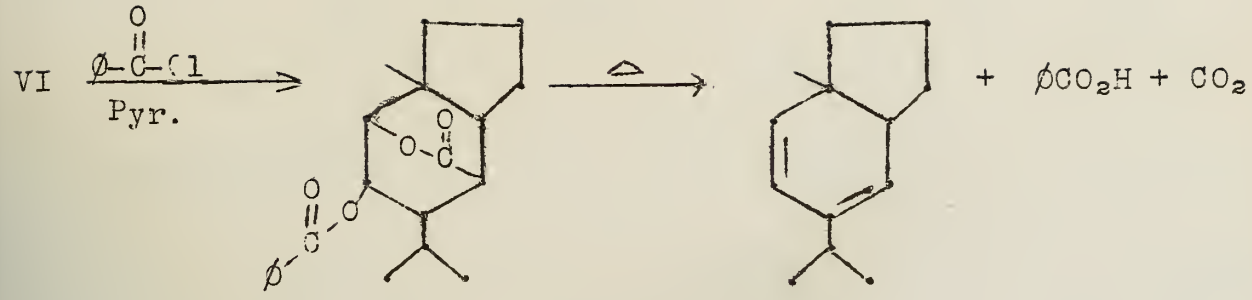
IV

Dihydropicrotoxinide

IV $\xrightarrow[\substack{HCl \\ CHCl_3}]{HSCH_2CH_2SH}$  $\xrightarrow[\substack{CH_3CH_2OH \\ R.T.}]{Ni(R)}$ 

V VI

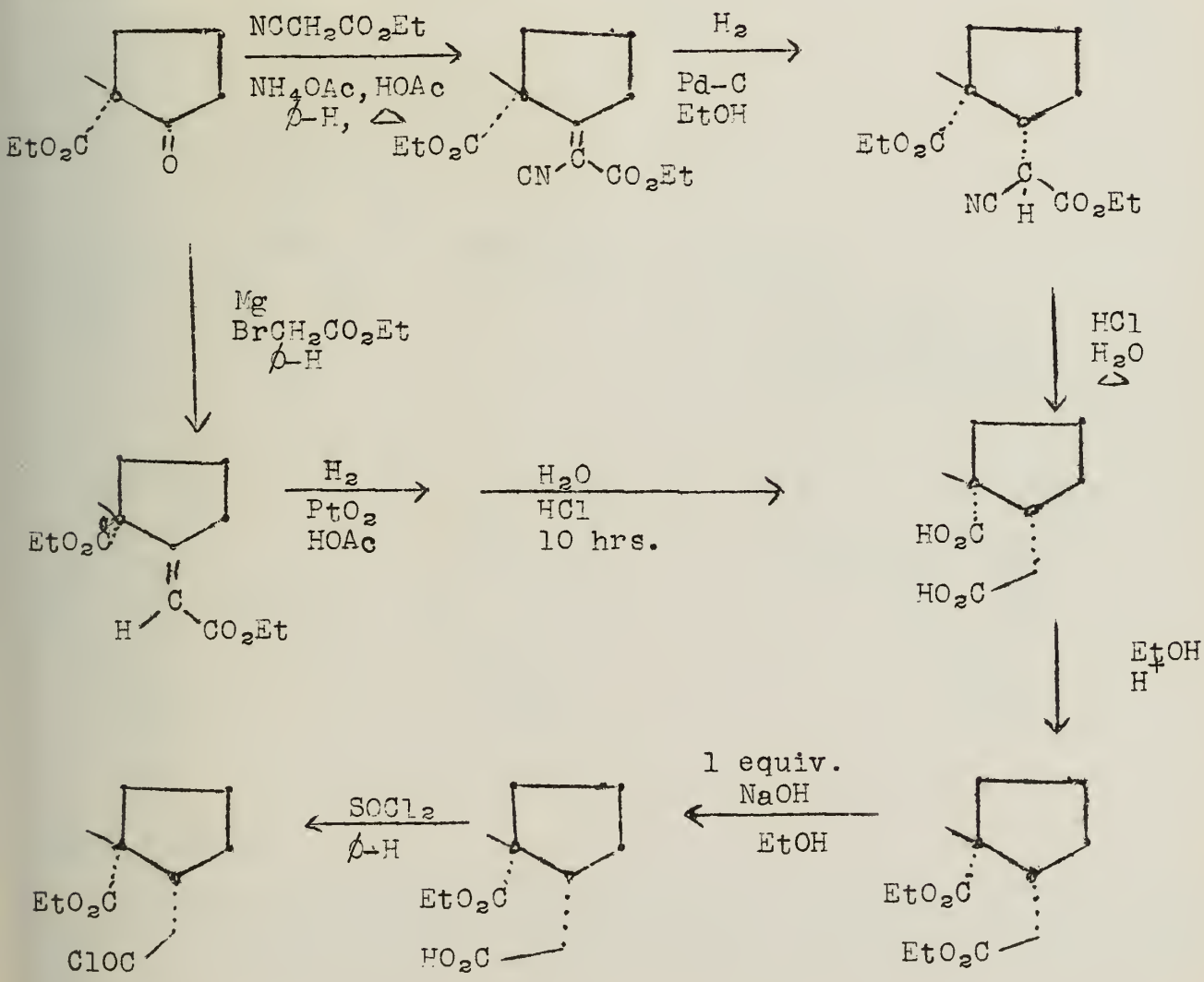
Tetrahydrodesoxypicrotoxinide



VII VIII

Picrotoxadiene

Synthesis of Picrotoxadiene



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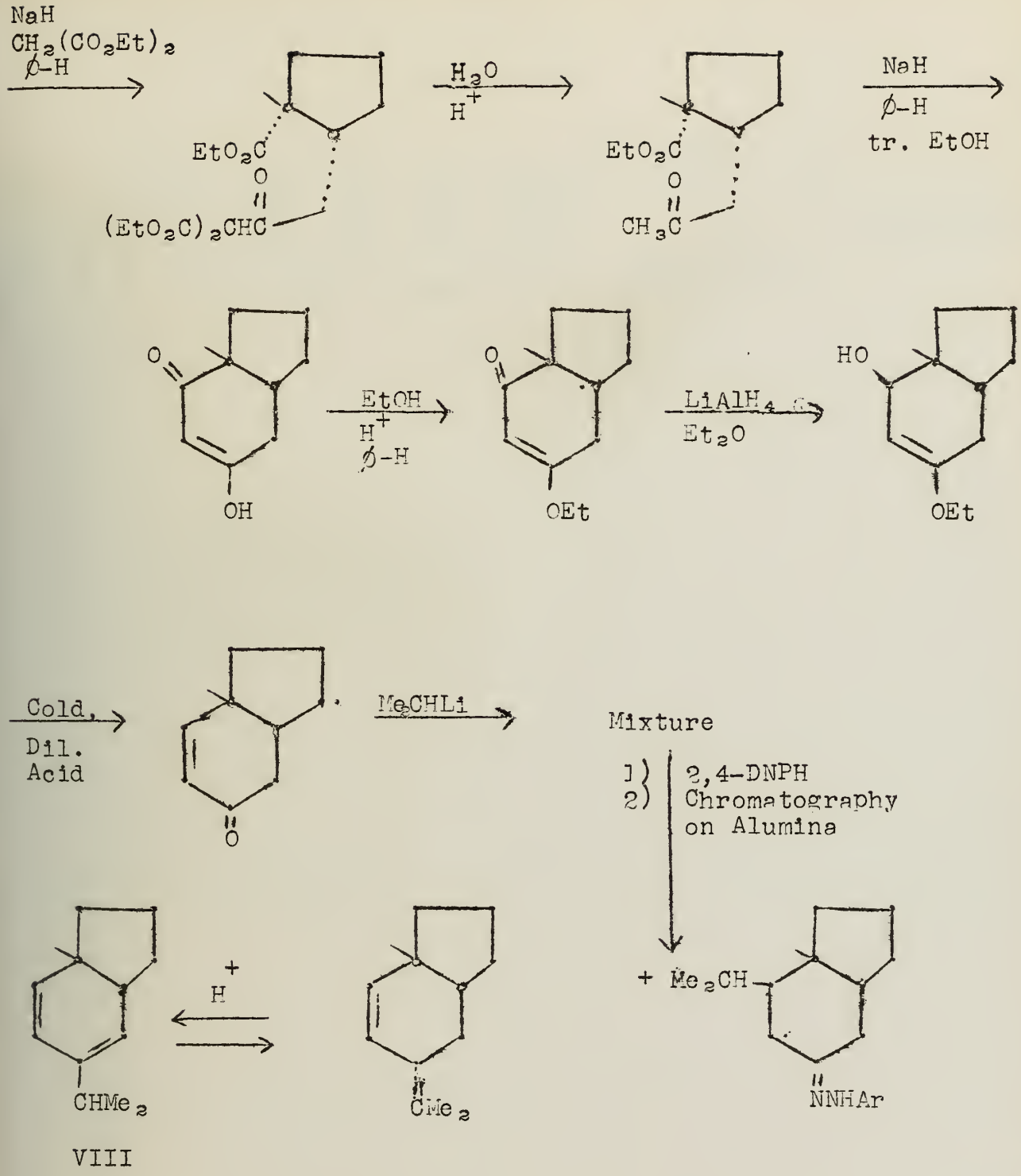

Other Workers

Slater, by means of a conductiometric titration study[5,6], provides additional evidence for a dilactone structure of picrotoxinin. Earlier, on the basis of infrared studies, he opposed such a structure, but later he reversed his stand as a result of further infrared studies.

On the basis of the failure of picrotoxinin to exhibit behavior of an ethylene oxide he also questions the ether linkage in structure II.

BIBLIOGRAPHY

1. H. Conroy, J. Am. Chem. Soc., 74, 491 (1952).
2. H. Conroy, ibid., 74, 3046 (1952).
3. H. Conroy, ibid., 73, 1889 (1951).
4. H. Conroy, ibid., 73, 1889 (1951).
5. S. N. Slater et al., J. Chem. Soc., 1952, 1042.
6. S. N. Slater, ibid., 1949, 806.

Sources for other reference

PINACOL-PINACOLONE REARRANGEMENTS

Reported by Ruth J. Adams November 14, 1952

Keeping in mind the conditions under which carbonium ions may be assumed to be generated, the pinacol rearrangements might properly be thought to belong to a family of pinacol-like rearrangements composed of the following reactions.

1. $R_2C(OH)-C(OH)-R_2 \xrightarrow{\text{acid}} R_3CC(=O)R$

2. $R_2C(OH)-CR_2(X) \xrightarrow{Ag^+} R_3CC(=O)R$ (X=halogen)

3. $R_2C(\overset{O}{\diagup\diagdown})-CR_2 \xrightarrow{H^+} R_3CC(=O)R$

4. $R_2C(OH)-CR_2(NH_2) \xrightarrow{\text{HONO}} R_3CC(=O)R$

5. $R_3CCHO \xrightarrow{\text{acid}} R_2C(H)-C(=O)-R$

Consequently, a great deal of what is known concerning one member of the above series can, with due restriction, be applied to the understanding of another related reation.

<u>Migration Aptitudes</u>.- The pinacol rearrangement was the subject of a group of experiments by Bachmann and co-workers. Given a symmetrical pinacol, that is, $R_1=R_3\neq R_2=R_4$, and basing their conclusions on the amount of each ketone isolated from the reaction

$$R_1-C(OH)(R_2)-C(OH)(R_3)-R_4$$

mixture, they found it possible to arrive at a set of values for the migration aptitudes of groups.

Some Migration Aptitudes Found by Bachmann

Pinacol	Groups	Migration %	Pinacol	Groups	Migration %
$[\underline{p}\text{-}CH_3C_6H_9(\phi)C(OH)]_2$	<u>p</u>-Tolyl	94	$[\underline{p}\text{-}CH_3O\text{-}C_6H_4(C_6H_4)C(OH)]_2$	Anisyl	98.6
	phenyl	6		Phenyl	1.4

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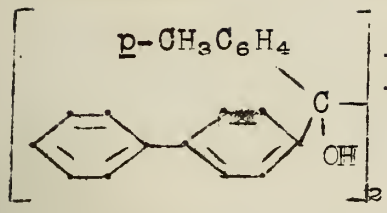
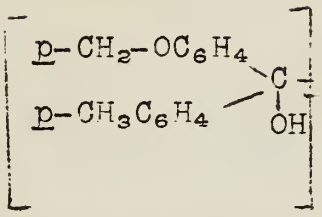
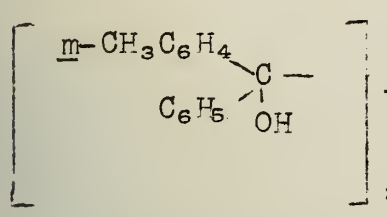
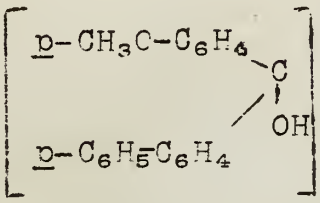
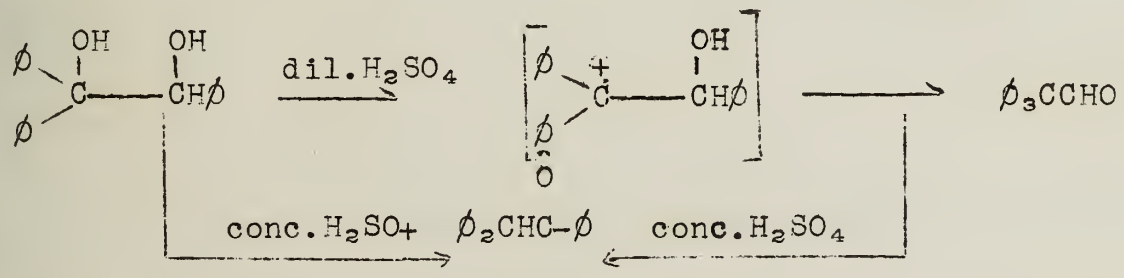
Pinacol	Groups	Migration %	Pinacol	Groups	Migration %
	p-Tolyl p-Biphenyl	57 43		Anisyl p-Tolyl	96.7 3.3
	m-Tolyl Phenyl	66 34		Anisyl p-Biphenyl	96. 3.

Quite recently, McEwen and Mehta[3] plotted the log of the migratory aptitudes obtained by Bachmann against Hammet's[4,5] sigma values [log of the ionization constant of the substituted benzoic acid minus the log of the ionization constant of benzoic acid] and have found good correlation. In other words, the ability of a substituent on the benzene ring to release or withdraw electrons from the ring is independent of the reaction which is being studied or the pinacol of which it is a part; and it is this characteristic which governs the outcome of the competition in migration of two groups in a symmetrical pinacol. As the table above shows, the phenyl with the more electron-releasing substituent is usually the one which migrates.

Kinetic vs. Thermodynamic Control.- Prediction of products of pinacol rearrangements is complicated by the fact that the carbonyl compound formed initially is sometimes unstable in the reaction medium. This easily could be resolved by preparing the carbonyl compounds expected and subjecting them to the conditions under which the rearrangement is carried out. If both were stable under the conditions imposed, then obviously the experiment had in reality measured the migratory aptitudes. However, if one ketone is converted to the other, then no conclusion could be drawn concerning the migratory aptitudes of the two groups. The work of Danilov and V. Danilova[2] is of value in this connection.



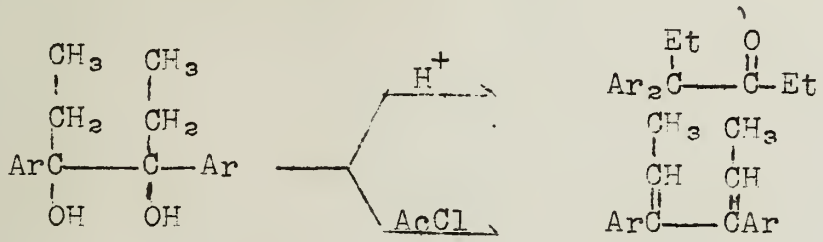
When the above rearrangement is carried out in conc.H_2SO_4, we have no assurance whatsoever, without further investigation, that the aldehyde is not formed initially and it, in turn, rearranges, due its thermodynamic instability in comparison to that of the ketone in the more drastic conditions.

Competing Oxide Formation.- Some interesting work by Lane and Walters[6] has been done on the pinacolic rearrangement of halohydrins

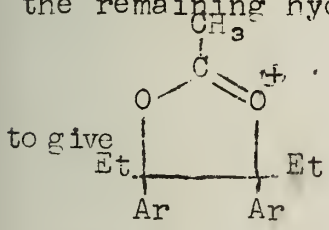
On treatment with silver nitrate, 2-bromo-1,1,2-triphenylethanol goes to the pinacolone. However, the reaction of the bromohydrin takes a different course when NaOH is used in place of silver nitrate and the epoxide is the product. On the basis of Winstein's[7] neighboring group theory, we see that $-O^-$ has a greater ability to displace bromine from the α-carbon than phenyl which, in turn, is better than -OH.

On the other hand, in a slightly more complex case, steric factors may cause deviations from what one expects from electric considerations only. K. Adams[9] has shown that tetraphenylethylene glycol is converted not only directly to the phenyltrityl ketone but also to tetraphenylethylene oxide. In this case, the hydroxyl can successfully compete with phenyl. Presumably this complication is caused by the strain arising from the crowding of three phenyls on one carbon as is the case when phenyl migrates. Therefore -OH is in a more favorable situation to compete with phenyl and some epoxide is formed.

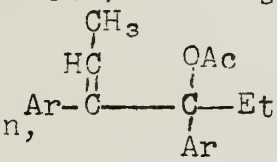
Competing Diene Formation.- The synthesis of the estrogen, 3,4-bis (p-hydroxy phenyl)-3,4-hexadiene is another remarkable example of the striking phenomenon of a change in the products of a reaction due to a change the medium in which it is conducted[8].



Only in acetylchloride does the dehydration take place. It has been postulated that the effect of acetyl chloride is due to initial esterification after which the potent neighboring group, $CH_3\overset{O}{\overset{\|}{C}}OO-$ displaces the remaining hydroxyl (as the conjugate acid)

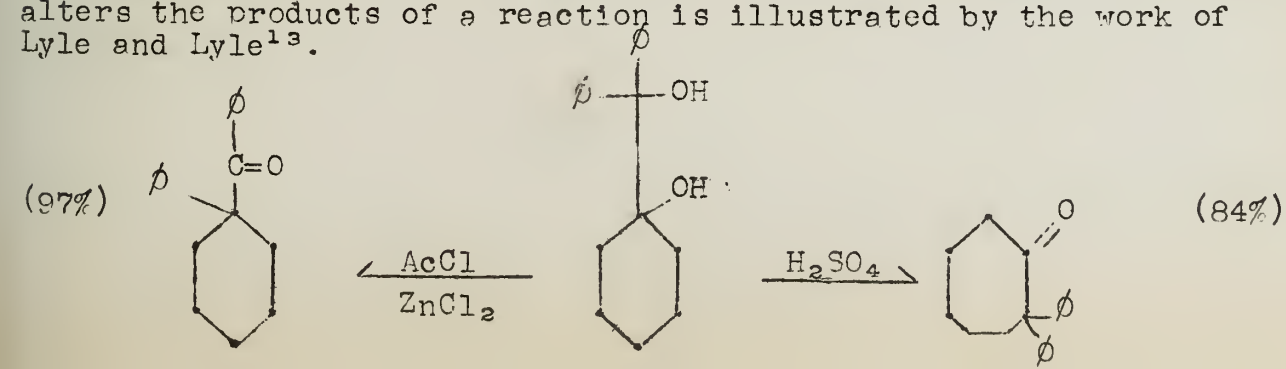


to give . On loss of a proton,



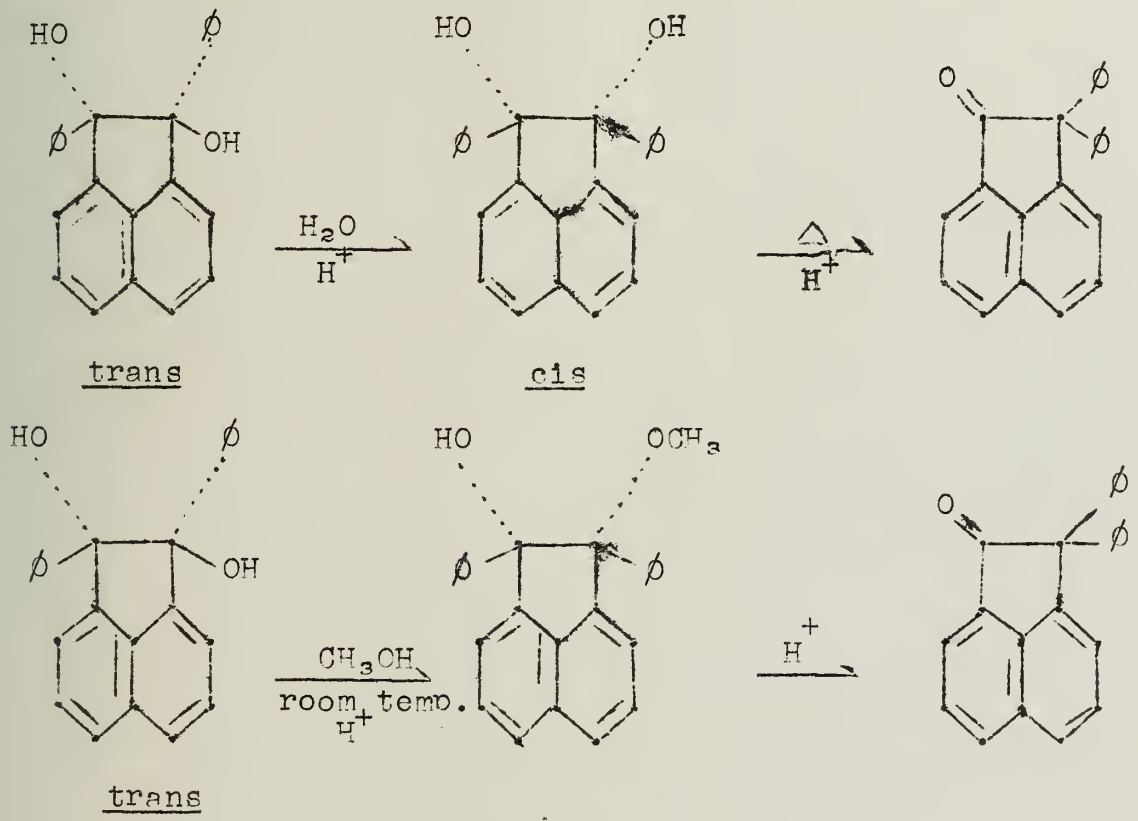
results which then splits off HOAc to give the diene.

Another case in which the use of acetyl choride as a solvent alters the products of a reaction is illustrated by the work of Lyle and Lyle[13].



The mechanism of this preferential arrangement has not been completely worked out.

Demonstration of Intermediate Ion.- The concept, not of a intermediate compound but of an intermediate ion, can clarify some of the experimental results that Criegee[10] and Bartlett and Brown[11,12] obtained. The rearrangement they observed was that of cis- and trans- 7,8-diphenylacenaphthene-7,8-diol. These structures excluded both ring contraction and simple dehydration. In anhydrous acetic acid, the cis-isomer rearranged to the pinacolone 3-6 times as fast as the trans-. The limiting rates of both isomers in considerable water were identical. This suggested a common intermediate. When the reaction of the trans-diol was halted, it was found to be a mixture of starting material, cis-diol and pinacolone. The indication is that water reacts with an intermediate ion to go back to cis-diol. Direct displacement of a protonated hydroxyl from the back by water seems unlikely for steric reasons. Brown has shown that alcohols can adopt the role of water with decreasing effectiveness as the bulk of the alkyl group is increased from CH_3 to Et- to i-Pr- to t-Bu.



BIBLIOGRAPHY

1. Bachmann and Moser, J. Am. Chem. Soc., 54, 1124 (1932); Bachmann and Ferguson, ibid., 56, 2112 (1934).
2. Daniloff and V. Danilova, Ber. 59, 377 (1926).
3. McEwen and Mehta, ibid., 74, 526 (1952).

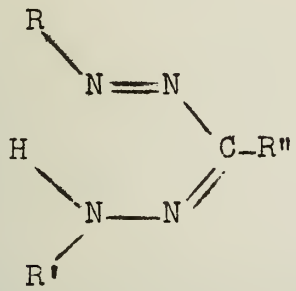
4. Hammett, L. Physical Organic Chemistry, p. 198, listed. (1940).
5. Organic Seminar Abstracts, University of Illinois, Dec. 7, 1951.
6. Lane and Walters, ibid., 73, 4234, 4238 (1951).
7. Winstein and Grunwald, ibid., 70, 828 (1948).
8. Lane and Spialter, ibid., 73, 4408, 4411 (1951).
9. Adams, K., Abstracts of Papers, 122nd Meeting of the American Chemical Society, 24M (1952).
10. Criegee and Plate, Ber. 72, 178 (1939).
11. Bartlett and Brown, J. Am. Chem. Soc. 62, 2927 (1940).
12. Brown, ibid., 74, 428, 432 (1952).
13. Lyle and Lyle, ibid., 74, 5059 (1952).

FORMAZANS

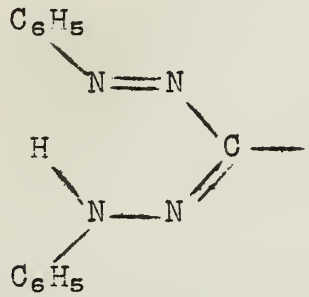
Reported by N. E. Bojars November 14, 1952

Introduction

A special class of the azo compounds consists of the formazans or formazyl derivatives (I).

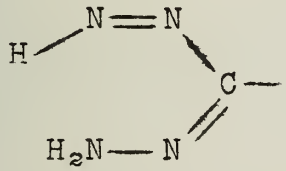


I

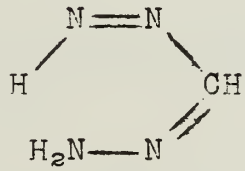


II

The name "formazyl" was originally introduced[1,2] for the radical (II). Later the name "formazyl" was proposed[3] for the unsubstituted radical (III).



III



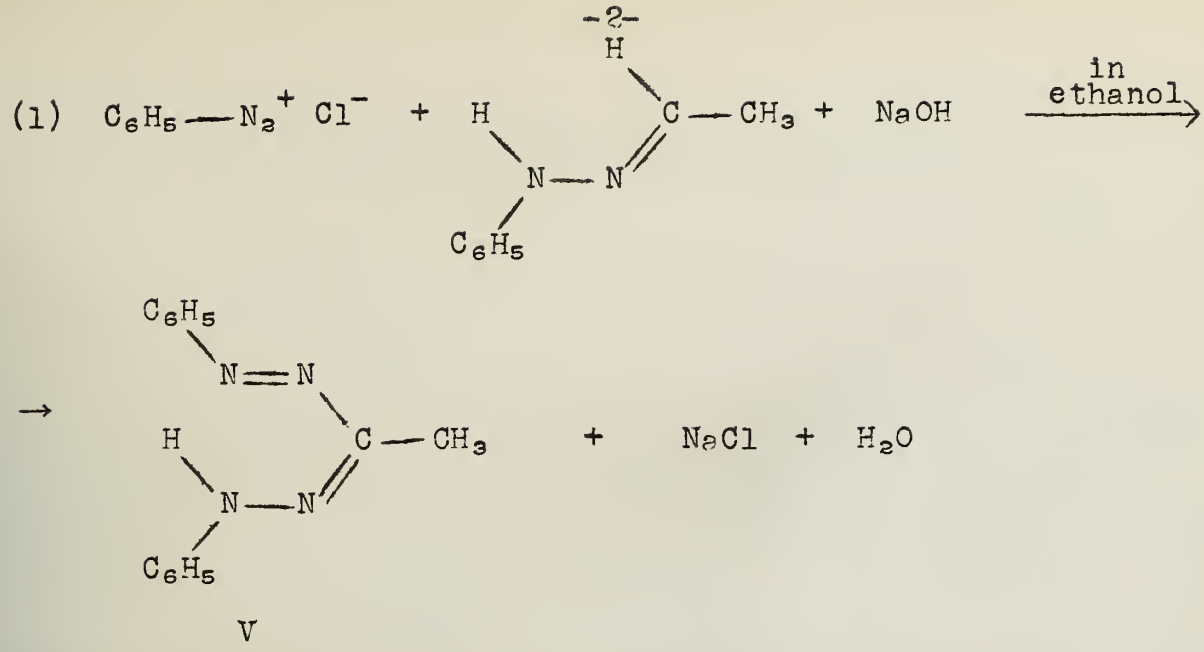
IV

However, in the modern literature still another basis of the nomenclature is employed[2,4,5] whereby the name "formazyl" is altogether discarded. All the compounds of this class are derived from the hypothetic parent compound formazan (IV).

Preparation of Formazans

The method of preparation, which has been most frequently employed, uses as the starting materials aldehyde phenylhydrazones and aromatic diazonium compounds. The attack of the diazonium group occurs upon the aldehyde carbon atom carrying the hydrazone group, with the elimination of a molecule of a halogen acid which reacts with alkali. An example is the reaction (1), producing[6] N,N'-diphenyl-C-methyl-formazan (V).

(1)



V

Several different methods of preparation are known[7,17].

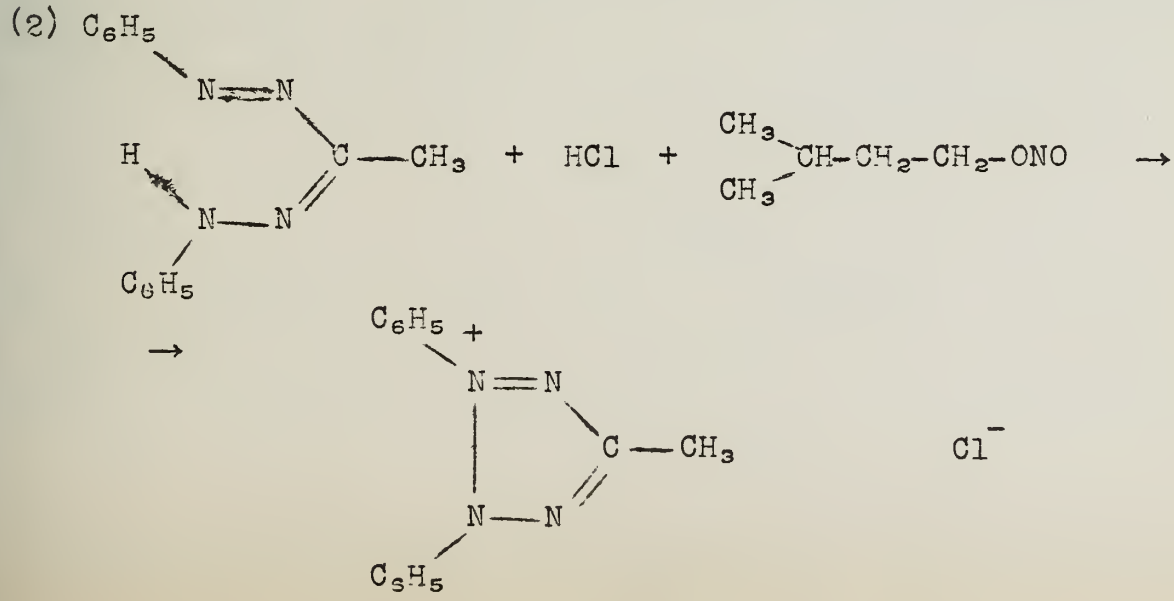
Properties and Reactions

Formazans are colored (mostly red) crystalline compounds. Most of them are stable at room temperature. They have the properties of dyes; some of them could be used to color wool and silk[18].

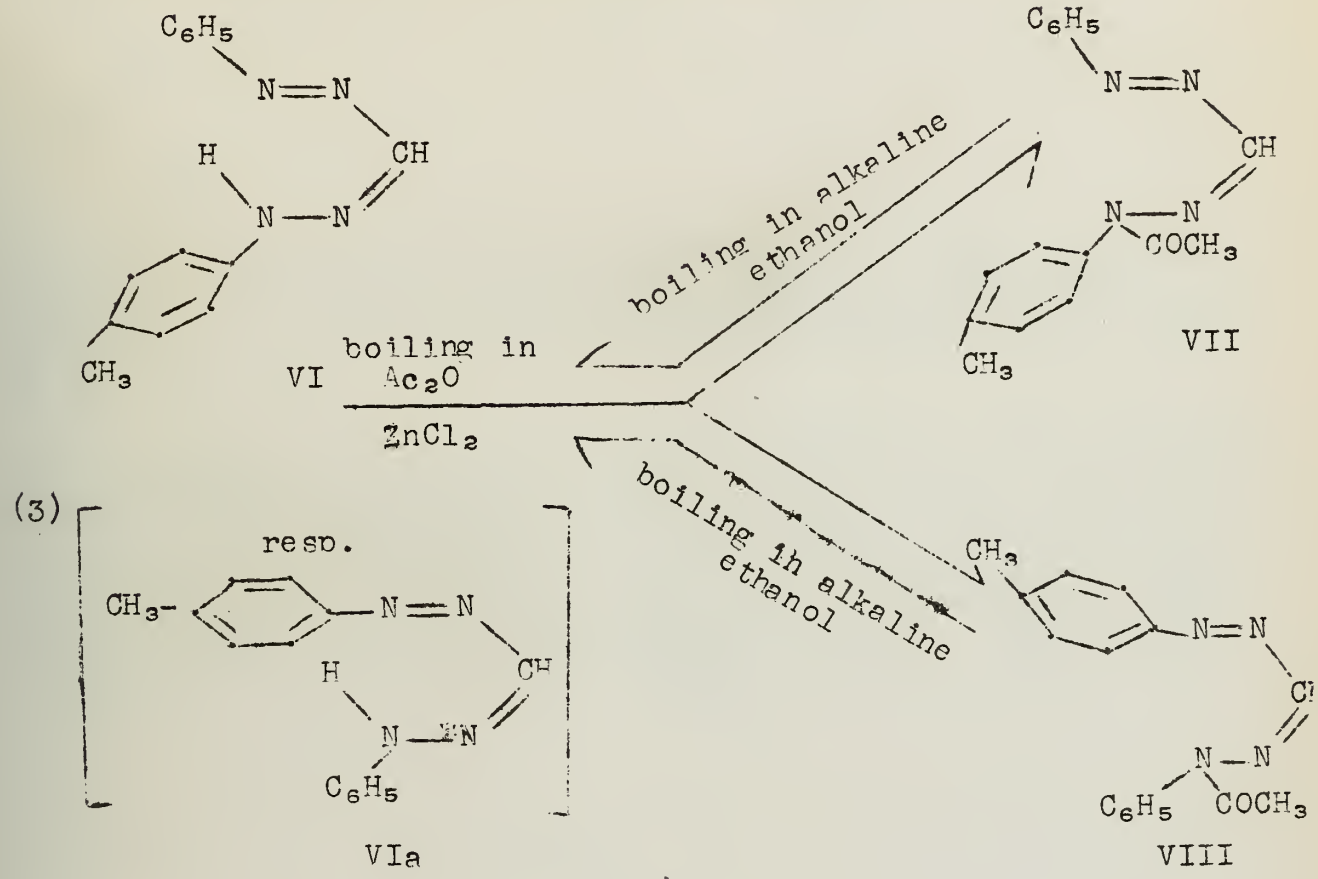
Because of the limited space only a few reactions of formazans can be mentioned here. Concentrated sulfuric acid dissolves the formazans with blue-green or green color[3,11,13,18,19] which usually becomes yellow or brown upon standing.

A characteristic reaction of the formazans is the oxidation to the tetrazolium salts[3,5,12,20]. An example[20] is the reaction (2), whereby N,N'-diphenyl-C-methylformazan is transformed into 2,3-diphenyl-5-methyltetrazolium chloride.

(2)



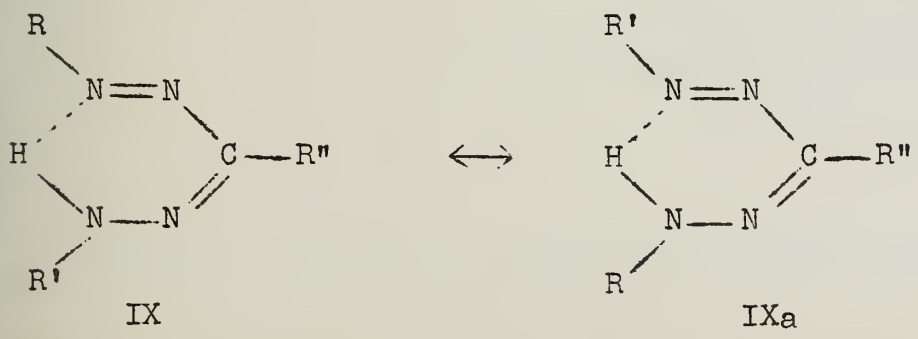
The N-hydrogen atom of the hydrazone group can be acylated; thi reaction can be reversed under certain conditions[13].



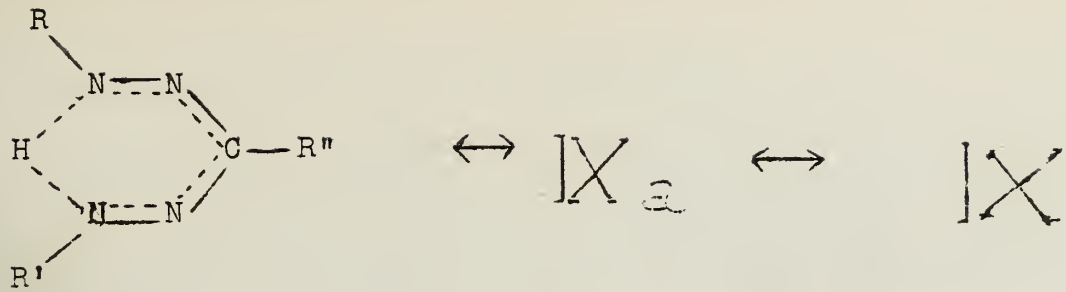
Tautomerism

In the reaction (3) the formulas VI and VIa represent one and the same compound[13]. Upon boiling with a little zinc chloride in acetic anhydride, two different compounds are formed in approximatel equal yields (VII and VIII).

Generally, compounds IX and IXa are identical[21,22].



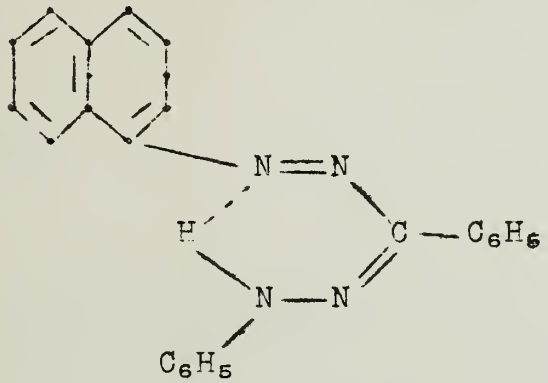
These are the mesomeric limiting states; perhaps the best representation of the average electronic density is the formulation IXb; there a dotted line represents a "half bond" (average in time).



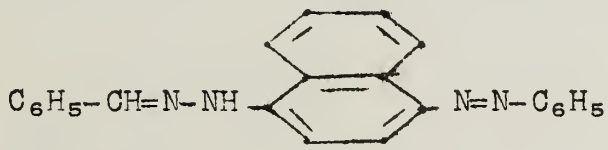
IXb

This formulation basically excludes the existence of isomers resulting by the exchange of R and R'. However, a few workers have announced that they have found isomeric formazans[18,23-27]. This introduced a seeming contradiction in the question of the structure of the formazans.

In the most cases no isomers were found[28-32]. This contradiction was solved[33] only quite recently. It was proved[33] that the isomers,[18,23-26] supposedly resulting by exchanging R and R' in the formula I, are isomers resulting by the attack of the diazonium group either upon the aldehyde carbon atom, as expected, or upon the aryl group of the aryl hydrazone part of the molecule. Examples of such isomers are the compounds X and XI. Only X is a formazan[33], while XI is an azo compound isomeric with it.



X

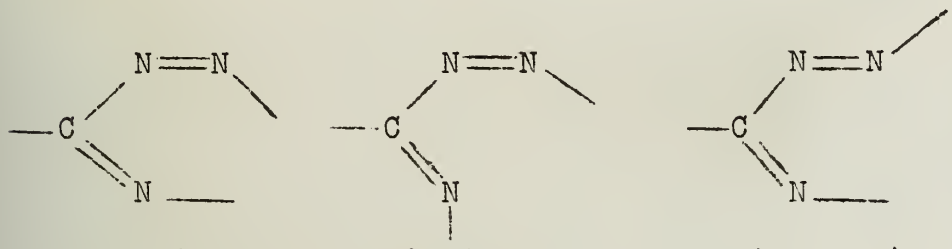


XI

Thus the structure of formazans involving the hydrogen bond seems to be now definitely proved.

The Red and Yellow Forms of the Formazans

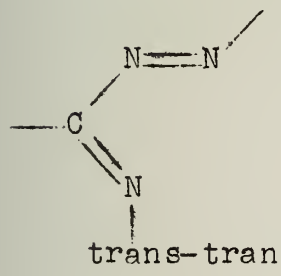
The solutions of formazans usually have a red color in benzene and similar organic solvents. The red solution of the formazan becomes yellow by the action of the visible light. Recently attemp have been made[33,34] to clarify the reason for this reversible chang of the color. Classically possible are four geometrical isomers (XII, XIII, XIV, and XV).



cis-cis XII

cis-trans XIII

trans-cis XIV



trans-trans XV

Since the yellow form is stable only in certain solvents or only under continuous illumination, it is supposed[34] that the yellow form is a geometric isomer richer in energy, and, therefore, less stable thermodynamically. The question has not been yet decided as to which of the cis-trans isomers is the yellow form. The problem is complicated by the question of whether the hydrogen bond is broken or not at the yellow $\rightleftharpoons$ red transitions.[34]

Bibliography

1. v. Pechmann, Ber. 25, 3177 (1892).
2. Bamberger, ibid., 25, 3207 (1892).
3. v. Pechmann, ibid., 27, 1683 (1894).
4. Wedekind, ibid., 31, 474 (1898).
5. Wedekind, ibid., 30, 444, 446 (1897).
6. Bamberger and Pemsel, ibid., 36, 54, 87 (1903).
7. v. Pechmann, ibid., 25, 3186 (1892).
8. Claisen, Ann. 287, 368 (1895).
9. Walther, J. prakt. Chem. [2] 53, 475 (1896).
10. Dains, Ber. 35, 2502 (1902).
11. Bamberger and Wheelwright, ibid., 25, 3204 (1892).

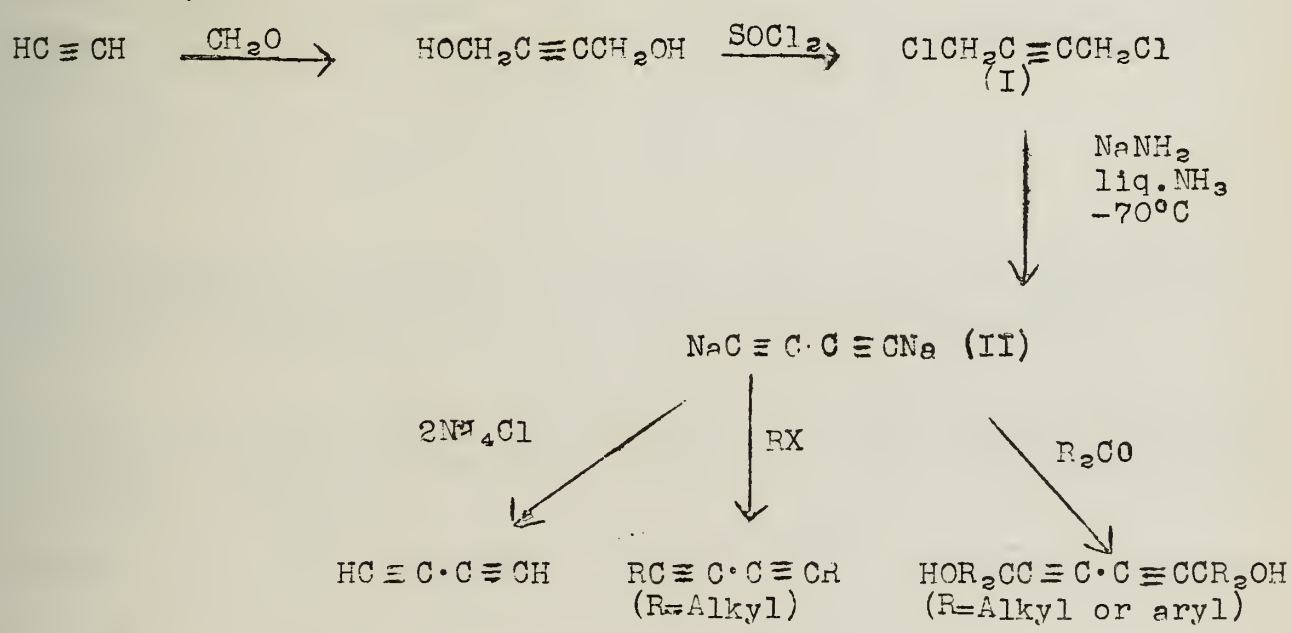
12. v. Pechmann and Runge, ibid., 27, 2927 (1894).
13. v. Pechmann and Runge, ibid., 27, 1698 (1894).
14. Bamberger and Billeter, Helv. chim. Acta 14, 219 (1931).
15. Pinner, Ber. 17, 183 (1884).
16. Bamberger, ibid., 27, 162 (1894).
17. v. Pechmann, ibid., 27, 322 (1894).
18. Fichter and Schiess, ibid., 33, 747 (1900).
19. Fichter and Schiess, ibid., 33, 749 (1900).
20. Wedekind and Stauwe, ibid., 31, 1756 (1898).
21. v. Pechmann, ibid., 27, 1682 (1894).
22. Lapworth, J. Chem. Soc. 83, 1119 (1903).
23. Fichter and Froehlich, Chem. Zetr. 1903 II, 427.
24. Ragno and Oreste, Gazz. chim. ital. 78, 228 (1948).
25. Fichter and Froehlich, Ztschr. Farb. Text. Chem. 2, 251 (1903).
26. Busch and Schmidt, J. prakt. Chem. [2] 131, 182 (1931).
27. Ragno and Bruno, Gazz. chim. ital. 67, 485 (1946).
28. v. Pechmann, Ber. 27, 1679 (1894).
29. v. Pechmann, ibid., 28, 876 (1895).
30. Marckwald and Wolff, ibid., 25, 3116 (1892).
31. Kuhn and Jerchel, ibid., 74, 941 (1941).
32. Hunter and Roberts, J. Chem. Soc. 1941, 820.
33. Hausser, Jerchel, and Kuhn, Ber. 84, 651 (1951).
34. Hausser, Jerchel, and Kuhn, ibid., 82, 515 (1949).

DI- AND POLYACETYLENES

Reported by Aldo J. Crovetti, Jr. November 14, 1952

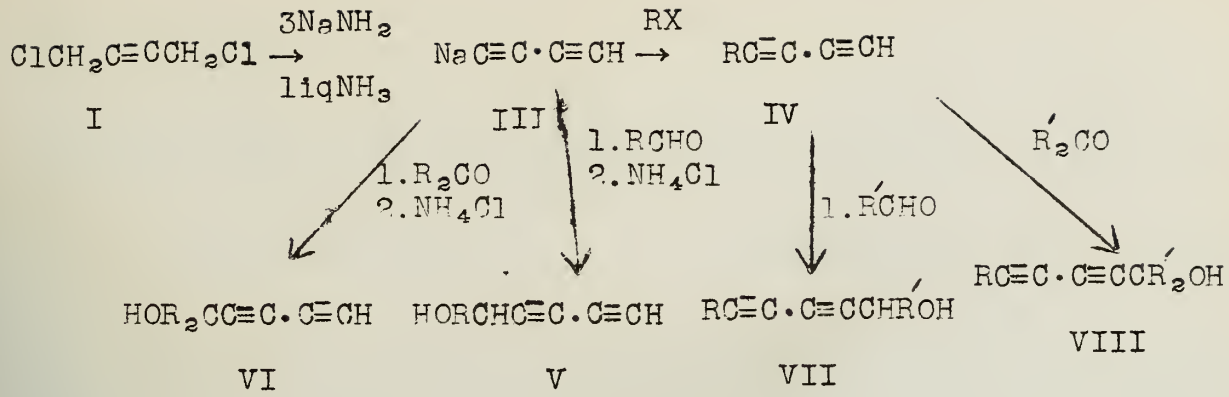
Polyacetylenes have created interest in different fields of chemistry. Because of their natural occurrence in essential oils from species of composites[1], in some Basidiomycetes, and the possibility of correlating light absorption properties with structure, the polyacetylenes have aroused the interest of the biochemist. The theoretical chemist has been intrigued because of their linear structure and consequent simple geometry. From the standpoint of organic chemistry they have been recognized as potential sources of many compounds.

DIACETYLENES: Diacetylene itself has been known for many years, but its use has been limited because of the difficulty of its preparation in quantity. The most useful laboratory method used involves oxidative coupling of monosodio acetylide[2] to give diacetylene (35%). The most promising route to diacetylene and higher diacetylenes seems to be from 1,4-dichloro-2-butyne[3] which is now commercially available from the cheap sources, acetylene and formaldehyde.



Until recently, contrasted to the many symmetrically substituted diacetylenes, mono-substituted diacetylenes were only four in number: 2-methyl-hexa-3,5-diyne-2-ol[4]; penta-1,3-diyne[2]; phenyl diacetylene and 1-iodoacetylene[5]. In addition to those the existence of methyl, ethyl and vinyl diacetylene has been detected in the high boiling residues from the Hüls acetylene synthesis process[6].

By using three molecular proportions of sodium amide, the monosodio diacetylide is presumed formed which upon alkylation with an alkyl halide gives rise to monoalkyl diacetylenes (IV).



The compounds (IV; R=Me, Et, Bu, $CH_2{=}CHCH_2$-) have been made in fair (45%) yields[7].

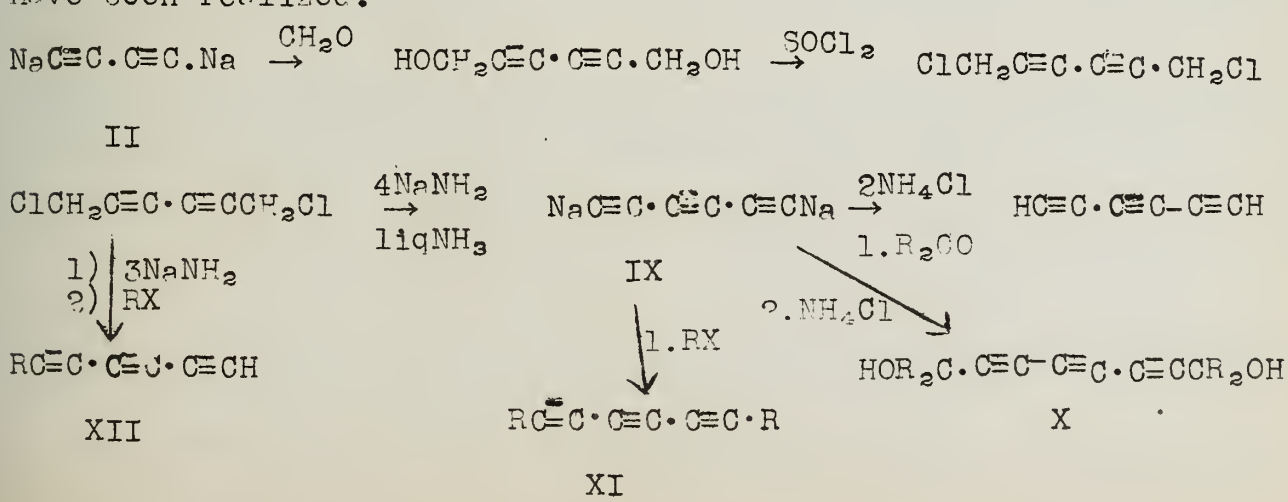
The reaction of carbonyl compounds such as acetaldehyde, butyraldehyde, acetone, benzophenone with the monosodio compound (III) gives compounds of the type (V) and (VI) respectively. Similarily, the monoalkyl diacetylene (IV) reacts to give compounds of the type (VII) and (VIII).

A number of 4-alkyl-1-iodo diacetylenes have been made by an extention of Vaughn's[8] method, which involves the iodination of a monalkyl acetylene in anhydrous liquid ammonia.

$$\underset{\text{IV}}{RC{\equiv}C\cdot C{\equiv}CH} + I_2 + NH_3 \rightarrow RC{\equiv}CI + NH_4I$$

<u>TRIACETYLENES</u>: Substances containing more than two conjugated acetylenic linkages have been almost unknown until recently. Diphenyl triacetylene and the glycol[9] have been described.

The analogy between the behavior of 1,4-dichloro-2-butyne and vicinal dihalides towards sodium amide in liquid ammonia has been extended[11] to 1,6-dichloro-hexa-2,4-diyne. The analogous reactions have been realized.



The compounds (X; R=Me,Ph), (XI; R=Me, Et), and (XIII; R=Me) have been prepared.

TETRACETYLENES: Until recently the only recorded example of a conjugated tetracetylenic compound was the highly unstable dicarboxylic described by Baeyer[12].

$$RC{\equiv}C\cdot C{\equiv}C\cdot C{\equiv}C.C{\equiv}C\cdot R \qquad\qquad HOR_2C\cdot C{\equiv}C.C{\equiv}C\cdot C{\equiv}C\cdot C{\equiv}C\cdot CR_2OH$$

XIII XIV

The previous method discussed has been found to be unsatisfactory for the preparation of compounds of type (XIII) and (XIV). The coupling action of potassium ferricyanide and potassium permanganat on the preformed copper diacetylide has proved unsuccessful[13]. However, the action of oxygen, in the presence of cuprous and ammonium chloride, cuprous bromide or iodine, on the Grignard derivative has given good yields (66%) of the crystalline deca-2, 4,6,8-tetrayne;

$$CH_3C{\equiv}C\cdot C{\equiv}CH \xrightarrow{EtMgX} CH_3C{\equiv}C\cdot C{\equiv}CMgX \xrightarrow{I_2} CH_3C{\equiv}C\cdot C{\equiv}C\cdot C{\equiv}C\cdot C{\equiv}C\cdot CH_3$$

$$RC{\equiv}C\cdot C{\equiv}CH \xrightarrow{EtMgX} RC{\equiv}C\cdot C{\equiv}C.MgX \xrightarrow{I_2} RC{\equiv}C\cdot C{\equiv}C\cdot C{\equiv}C.C{\equiv}C.R$$

XV

Analogous methods enabled the compounds (XV; R=Et, Bu) to be made. In this series there is a decline in the melting point as the series is ascended. This has been attributed to an abrupt decrease in symmetry from the rigidly linear molecule (XV; R=Me) to the Z shaped molecule of (XV; R=Bu). There have been indications that the latter also possesses the ability of rotation in the solid state[13].

The use of the Grignard derivative to make tetra-acetylenic alcohols is unsuccessful. The compounds (XV; $R=CH_2OH$) and (XV; $R=CMe_2OH$) were obtained in 74% and 89% yields respectively by a catalytic oxygenation coupling of the respective monosubstitute diacetylenic alcohols.

HIGHER POLYACETYLENES: Attempts have been made to develop routes of general applicability for compounds with more than four conjugated acetylene linkages and some progress has been made.[14]

$$HOCH_2(C{\equiv}C)_nCH_2OH \quad ClCH_2(C{\equiv}C)_nCH_2Cl \quad H(C{\equiv}C)_nH \quad CH_3(C{\equiv}C)_nCH_3$$

XVI XVII XVIII XIX

a) The conversion of (XVI; n=1,2,3) into (XVII; n=1,2,3) indicates a possible route to higher poly-ynes by the scheme:

$$HOCH_2(C{\equiv}C)_nCH_2OH \xrightarrow{SOCl_2} ClCH_2(C{\equiv}C)_nCH_2Cl \xrightarrow[-77^\circ]{NaNH_2} H(C{\equiv}C)_{n+1}H$$

The glycol (XVI; n=3) treated in this manner, followed by extraction with pentane gave a solution which when examined spectroscopically gave evidence for octa-1,3,5,7-tetrayne (XVIII; n=4) at an estimated yield of 12%. In a similar way the glycol (XVI; n=4) gave a solution which when examined spectroscopically gave bands expected for deca-1,3,5,7,9-pentayne in an estimated 1% yield[14]. As (n) increases the yields in the process XVI → XVII → XVIII fall decidedly from nearly quantitative (n=2) through about 50% (n=3), and about 12% for (n=4) to about 3% for (n=5). Modification of reaction conditions seems necessary before this general method can be extended.

b) The complimentary route indicated below thus far has proved fruitful only in the case where R=Ph and Me when (n=3).

$$RCH(OH)(C{\equiv}C)_{n-1}CH(OH)R \xrightarrow{SOCl_2} RCHCl(C{\equiv}C)_{n-1}CHClR \xrightarrow{NaNH_2} \underset{XX}{R(C{\equiv}C)_nR}$$

In the case (XX; n=3, R=Me) a 56% yield was obtained in contrast to that previously obtained by alkylation (28%).

c) Of potential value is the alternative method of obtaining monosubstituted polyacetylenic hydrocarbons of primary-secondary glycols. The latter are prepared by condensation of a carbonyl compound with a compound of the type $XMg(C{\equiv}C)_nCH_2OMgX$

$$RCHO + MgX(C{\equiv}C)_nCH_2OMgX \xrightarrow{HX} RCH(OH)(C{\equiv}C)_nCH_2OH \xrightarrow[\substack{2.\,NaNH_2 \\ 3.\,NH_4Cl}]{1.\,SOCl_2} R(C{\equiv}C)_{n+1}H$$

In the case of hexaynes a short step process must be used e.g.

$$ClCH_2C{\equiv}C\cdot C{\equiv}C\cdot CH_2Cl \xrightarrow[CH_3I]{NaNH_2} CH_3C{\equiv}C\cdot C{\equiv}C{\equiv}C\cdot H \xrightarrow[2)\,I_2]{1)\,EtMgX} CH_3(C{\equiv}C)_6CH_3$$

Diethyl hexa-acetylene has been obtained in this way. Because of the photo-instability of these compounds their isolation is difficult. The diphenyl hexayne, however, has been prepared in good yield by a similar route[15].

$$\underset{Br}{PhCH{=}CCHO} + XMgC{\equiv}CCH_2OMgX \rightarrow \underset{Br}{PhCH{=}C\cdot CH(OH)C{\equiv}CCH_2CH} \xrightarrow[\substack{2.\,NaNH_2 \\ 3.\,NH_4Cl}]{1.\,SOCl_2} Ph(C{\equiv}C)_3H \xrightarrow[O_2]{CuCl} \underset{30\%}{Ph(C{\equiv}C)_6Ph}$$

PROPERTIES: The monoalkyl polyacetylenes are unstable compounds tending to volatilize easily and explode. The dimethyl polyacetylenes are all crystalline solids which decompose

(except n<4) on heating. As larger R groups are attached, the compounds tend to become more easily volitalized. They are not dangerously explosive (n<6). Those members in which n=>3 are very easily decomposed in the presence of light but in the dark they are much more stable. They are usually kept at -70°C, but all can be recrystallized form warm solvents. The diphenyl polyacetylenes are much more stable than the alkyl derivatives.

The glycols are all crystalline solids and appreciably more stable than the dimethyl poly-ynes. The primary and secondary glycols are very much less stable than the tertiary glycols.

The crystals which are photolabile give intensely colored pigments, usually a vivid red or blue. The most sensitive in this respect is the dichloride $ClCH_2(C{\equiv}C)_4CH_2Cl$, which surpasses AgBr, becoming dark blue on exposure to diffuse daylight for 10-30 seconds The process appears to be associated with the crystal lattice e.g. octa-3,5-diyne-1,8-diol is stable to light in liquid state, while in solution, above its melting point, or even as a super cooled liquid, yet a deep red color rapidly develops on the surface of the solid unless light is excluded[15]. The general nature of these irradiation products are similar amongst di- and polyacetylenes. They are amorphous films insoluble in organic solvents and immiscible with the fused parent acetylenic compound.

LIGHT ABSORPTION: In all cases observed the spectra of these compounds consists of a medium intensity region and a high intensity region as seen in figure I for the case of dimethyl poly-ynes (n=5,6).

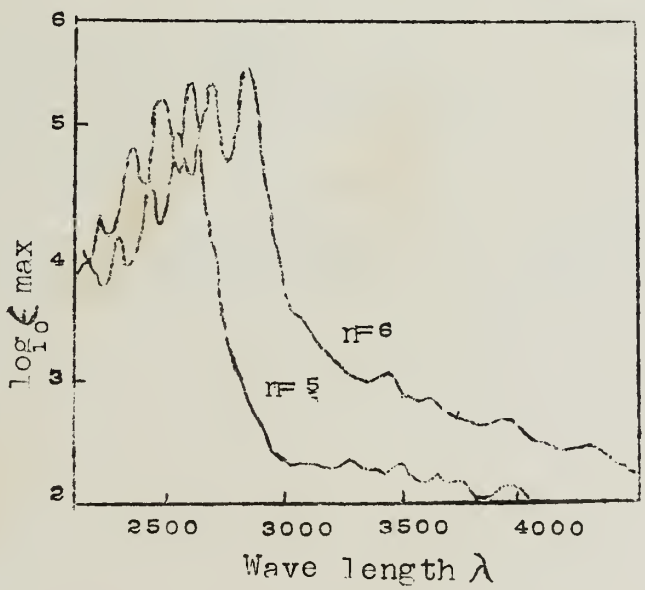


Figure I

The maxima show a spacing of 2,000-2,300 cm.$^{-1}$ The very high intensity in the case of the dimethyl poly-ynes where n=6, the ϵ max= 445,000 at 2840Å, is the second largest extinction coefficient yet reported[13]. However, the absorption intensity per unit weight ($E^{1\%}_{1cm}$), (XIX) n=6) exceeds all other substances by a factor approaching three; $E^{1\%}_{1cm}$ = 25,500 (XIX n=6), 2840 Å. That known for anthracene is $E^{1\%}_{1cm}$ = 9,400 at 2510 Å previously regarded as the highest $E^{1\%}_{1cm}$ value.

BIBLIOGRAPHY

1. N. A. Sörensen and K. Stavholt, Acta. Chem. Scand., 4, 1567, 1575 (1950).
2. H. Schlubach and V. Wolf, Ann., 568, 141 (1950).
3. J. B. Armitage, E. R. H. Jones, and M. C. Whiting, J. Chem. Soc. 44 (1951).
4. Yu. S. Zalkind and M. A. Aizikovich, J. Gen. Chem. (U.S.S.R.) 9, 961 (1939); C. A. 33, 38695 (1939).
5. H. Schluback and V. Franzen, Ann., 573, 105, 115 (1950).
6. J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publishing Company, New York, 1949 p. 3, 121, 302.
7. J. B. Armitage, E. R. H. Jones and M. C. Whiting, J. Chem. Soc., 1993 (1952).
8. T. H. Vaughn and J. A. Neuland, J. Am. Chem. Soc., 55, 2150 (1933).
9. H. Schluback and V. Franzen, Ann., 572, 116 (1951).
10. F. Bohlmann, Angew. Chem., 63, 218 (1951); R. Kuhn, ibid. 173 (1951).
11. J. B. Arnitage, C. L. Cook, E. R. H. Jones, and M. C. Whiting, J. Chem. Soc. 2010 (1952).
12. A. Baeyer, Ber., 18, 2272 (1885).
13. J. B. Armitage, E. R. H. Jones, and M. C. Whiting, J. Chem. Soc., 2014 (1952).
14. C. L. Cook, E. R. H. Jones, and M. C. Whiting, ibid., 2883 (1952).
15. E. R. H. Jones, M. C. Whiting, C. L. Cook, and N. Entwistle, Nature, 168, 900 (1951).

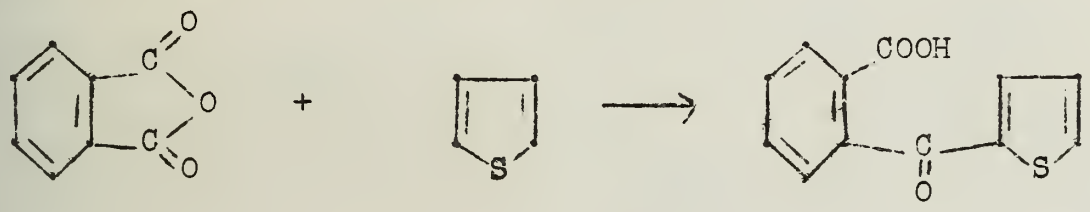
THENOYLBENZOIC ACIDS AND THIOPHANTHRAQUINONES

Reported by J. A. MacDonald November 21, 1952

It would appear possible to prepare from thiophanthraquinones a series of dyes analagous to the anthraquinone dyes. This possibility is responsible for at least a part of the interest recently shown in the synthesis of thiophanthraquinones. The general method employed for the synthesis of these compounds consists of the preparation of 2-(2-thenoyl)-benzoic acids and subsequent ring closure.

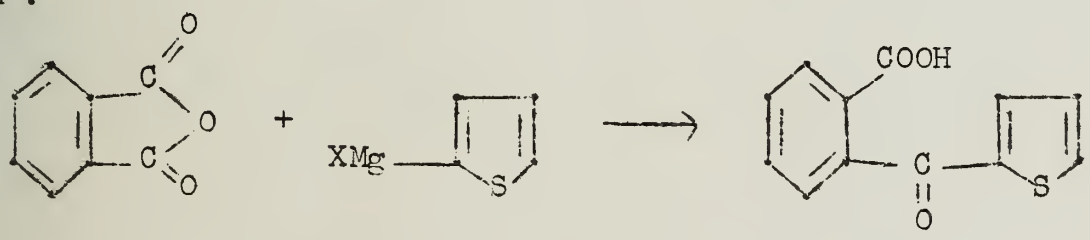
2-(2-Thenoyl)-benzoic Acids

2-(2-Thenoyl)-benzoic acid was first prepared by Steinkopf[1], who employed the reaction between phthalic anhydride and thiophene in the presence of aluminum chloride:



Buu-Hoi and co-workers[2], starting from 2-methyl-, 2-chloro-, and 2-bromothiophene, used the same method for the preparation of 2-(2-thenoyl)-benzoic acids substituted in the 5 positon of the thiophene ring.

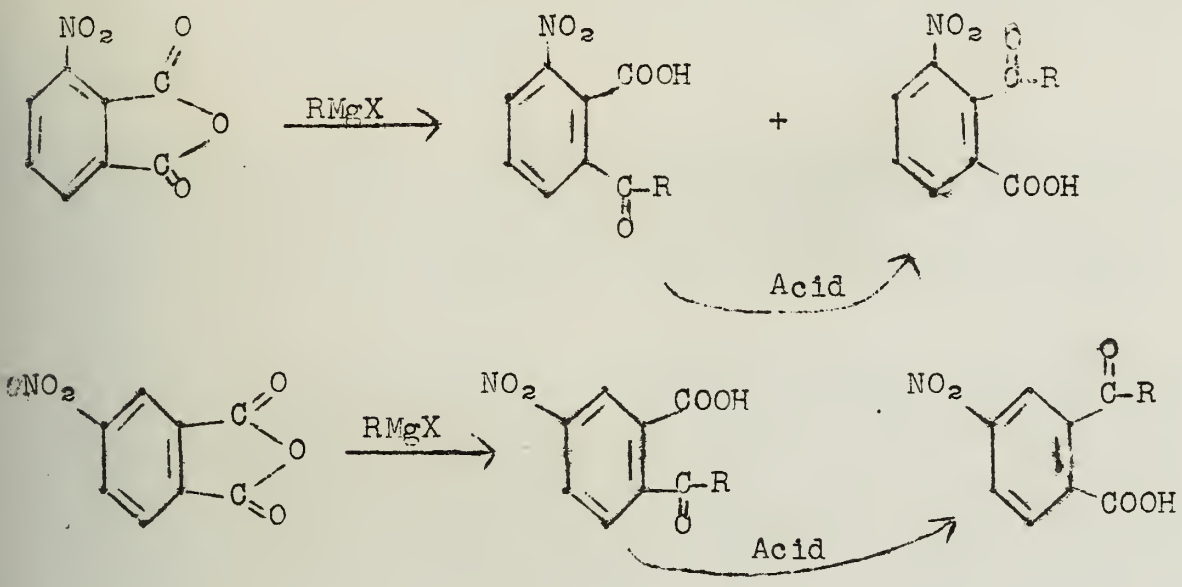
A different method, consisting of the action of 2-thienylmagnesium iodide on phthalic anhydride, was used by Goncalves and Brown[3]:



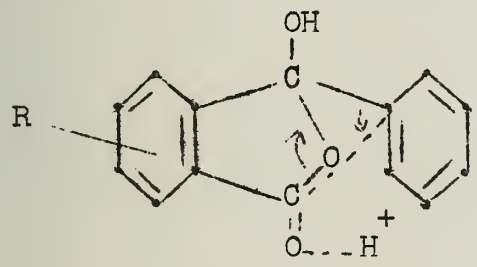
They investigated various solvents and temperatures for the reaction, and found that the use of anisole as solvent, at a temperature below 27° gave the best results. A 90% yield was obtained. The Grignard method was also applied to the preparation of 2-(2-thenoyl)-benzoic acids with methyl, ethyl, chloro and bromo substituents in the 5 position of the thiophene ring.

Working independently, Lee and Weinmayr[4] employed the Grignard method for the preparation of 2-(2-thenoyl)-benzoic acids with haloger atoms or nitro groups substituted in the benzene ring. They found that the action of thienylmagnesium halides on unsymmetrically substituted phthalic anhydrides yielded both of the possible isomeric products. Brown and co-workers[5] also investigated the synthesis of nitro-2-(2-thenoyl)-benzoic acids by the Grignard method, but found

at first that only one of the possible isomers was obtained from each of the mono nitro phthalic anhydrides. A closer investigation showed, however, that both products were produced in the reaction, and that in the purification by recrystallization from acetic acid one of the products was converted into the other. The conversion could also be effected by the use of concentrated sulfuric acid.



Rearrangements of this type have been observed and investigated in 2-benzoylbenzoic acids[6,7], and it has been suggested that the lactol form of the acid (I) is an intermediate.



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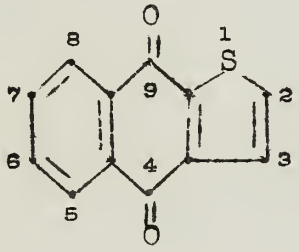


II

The structures of the nitro-2-(2-thenoyl)-benzoic acids were determined by decarboxylation and comparison of the resulting ketones with the compounds obtained from the reactions of nitrobenzoyl chlorides with benzene.

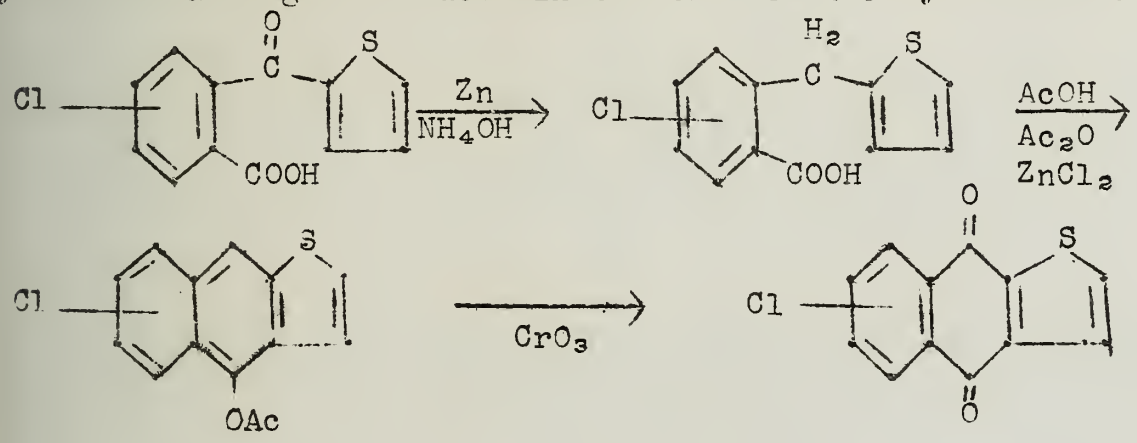
Weinmayr[8] reinvestigated the Friedel-Crafts synthesis of 2-(2-thenoyl)-benzoic acids, and obtained satisfactory yields when phthalic anhydride was condensed with thiophene or various substituted thiophenes. The reaction was, however, not satisfactory for the condensation of thiophene with chloro- or nitrophthalic anhydrides. In these cases excellent results were obtained by use of the reaction of 2-thienylmagnesium bromide with the anhydrides. The constitutions of the chloro-2-(2-thenoyl)-benzoic acids were determined by relating them to the nitro-2-(2-thenoyl)-benzoic acids through the conversion of the latter to the former by reduction and use of the Sandmeyer reaction.

Thiophanthraquinones

Steinkopf[1] found that treatment of 2-(2-thenoyl)-benzoic acid with phosphorus pentoxide or concentrated sulfuric acid yielded thiophanthraquinone (II). When sulfuric acid was used there was obtained, in addition to this compound, a water soluble acid presumed t be a sulfonic acid derivative of the quinone. When this acid was fused with alkali an orange-red product, possibly the thiophene analo of alizarin, was obtained.

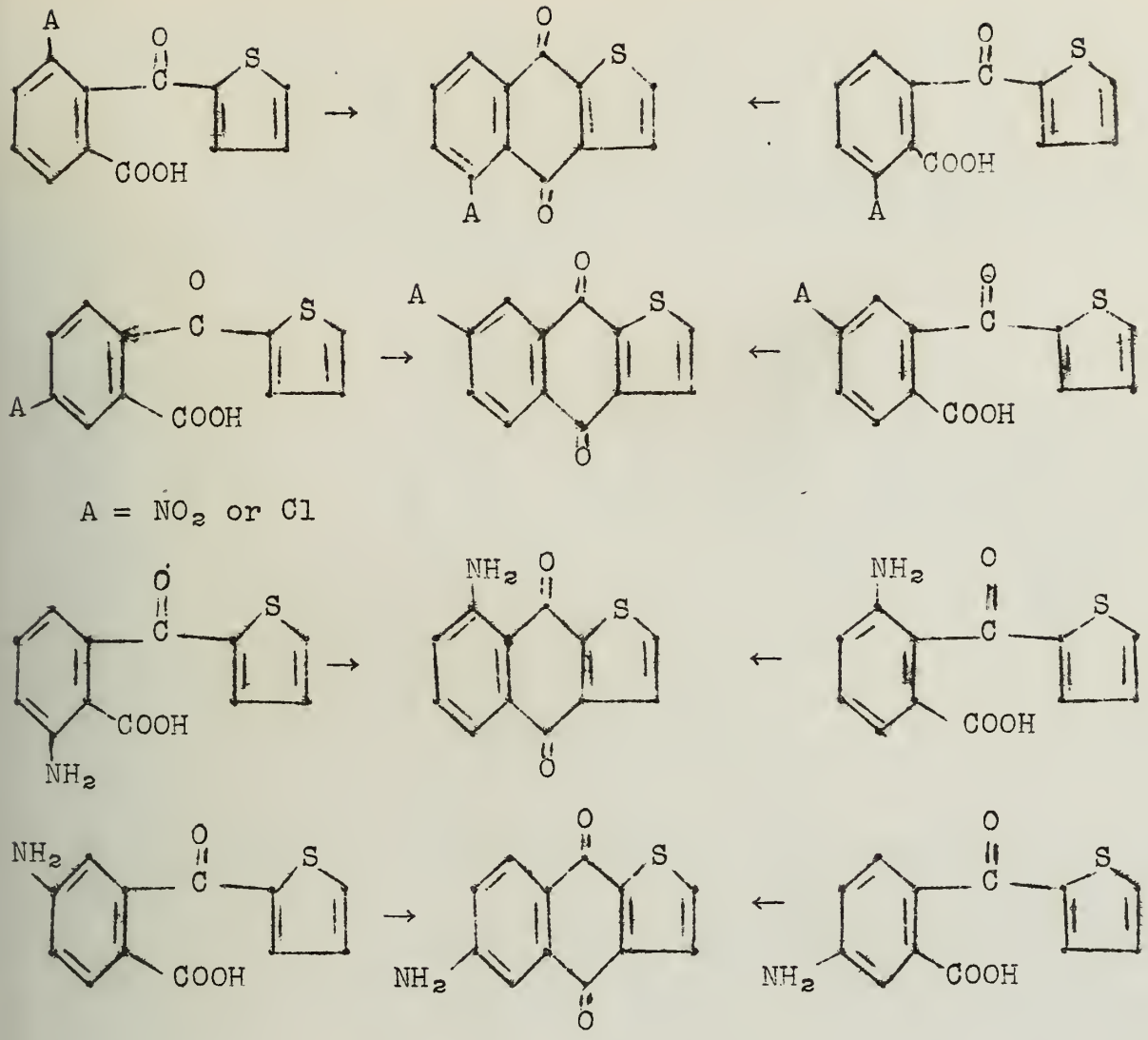
Buu-Hoi[2] carried out the cyclization using benzoyl chloride as the dehydrating agent. Brown[3,5] and Weinmayr[8,9] have prepared many substituted thiophanthraquinones by ring closure of the corresponding 2-(2-thenoyl)-benzoic acid chlorides, and also by the direct ring closure of the acids through the use of phosphorus pentoxide, sulfuri acid and aluminum chloride.

From the ring closure of the four isomeric 2-(2-thenoyl)-benzoic acids monosubstituted in the benzene ring, four thiophanthraquinones would be expected. However, in the cases investigated[9], only two were obtained, indicating that rearrangement occurred in at least some of the ring closures. In order to establish the identity of the thiophanthraquinones obtained, the four monochloro benzene substituted thiophanthraquinones were prepared by the following method, known to yield unrearranged products in the case of 2-aroylbenzoic acids[10].



The chlorothiophanthraquinones were used as reference compounds in the identification of the other thiophanthraquinones.

When the products of cyclization had been identified, it was apparent that mono substituted thenoylbenzoic acids with nitro or chloro groups meta to the thenoyl group cyclized normally, while those with either of these groups in an ortho or para position rearranged. Conversely, when an amino group was ortho or para to the thenoyl group cyclization was normal, while the meta derivatives rearranged:

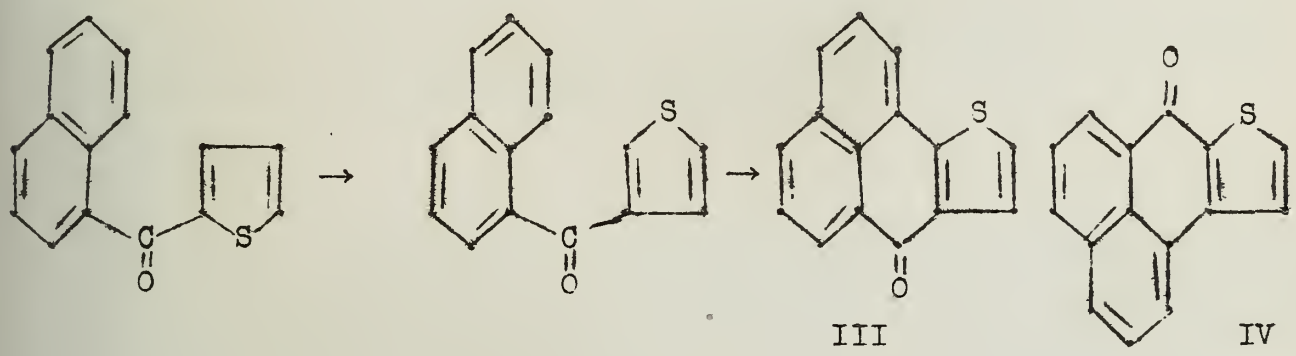


It would appear that the products obtained could be accounted for by rearrangements of the type mentioned previously, in which the thenoyl and carboxyl groups of thenoylbenzoic acids are interchanged. However, at least in the case of 3-nitro-2-(2-thenoyl)-benzoic acid, some evidence that the rearrangement involved is a different one was provided by the fact that on treating this acid with 100% sulfuric acid, a rapid rearrangement to another acid, different from 6-nitro-2-(2-thenoyl)-benzoic acid, occurred. It has been suggested that the rearrangement involves a shift of the nitrophthaloyl radical from the 2- to the 3- position of the thiophene to yield 3-nitro-2-(3-thenoyl)-benzoic acid.

Benzthiophanthrones

Thiophanthraquinone can form two benzthiophanthrones (III and IV). Scholl and Seer[11] fused 1-(2-thenoyl)-naphthalene with aluminum chloride, and obtained what they assumed to be 4,5-benzthiophanthrone (IV). Recently Weinmayr and co-workers[12] repeated this synthesis, and also prepared a different benzthiophanthrone from the reaction of thiophanthraquinone with glycerol and iron in sulfuric acid. At first they believed this new product to be 8,9-benzthiophanthrone (III).

However, on oxidation it gave a thiophanthraquinone carboxylic acid the infrared spectrum of which was identical with the spectrum shown by thiophanthraquinone-5-carboxylic acid, and very different from the spectrum of thiophanthraquinone-8-carboxylic acid. The new benzthiophanthrone must therefore be 4,5-benzthiophanthrone, and it must be assumed that a rearrangement occurred during the aluminun chloride fusion of 1-(2-thenoyl)-naphthalene. The rearrangement shown below, similar to the one proposed in the case of 3-nitro-2-(2-thenoyl)-benzoic acid, has been suggested:



Bibliography

1. W. Steinkopf, Ann. 407, 94 (1914).
2. Ng. Ph. Buu-Hoi, N. G. Hoan, and N. G. D. Xuong, Rec. trav. chim. 69, 1083 (1950).
3. R. Goncalves and E. V. Brown, J. Org. Chem. 17, 698 (1952).
4. H. R. Lee and V. Weinmayr, U.S. Patent 2513573 (C. A. 45,665 (1951).); U.S. Patent 2513572 (C. A. 45, 664 (1951).).
5. R. Goncalves, M. R. Kegelman, and E. V. Brown, J. Org. Chem. 17, 705 (1952).
6. M. Hayashi, J. Chem. Soc. 2516 (1927); 1513, 1520, 1524 (1930); M. Hayashi et al., Bull. Chem. Soc. Japan 11, 184 (1936).
7. J. W. Cook, J. Chem. Soc. 1472 (1932).
8. V. Weinmayr, J. Am. Chem. Soc. 74, 4353 (1952).
9. H. E. Schroeder and V. Weinmayr, ibid. 74, 4357 (1952).
10. L. F. Fieser and E. B. Hershberg, ibid. 59, 1028 (1937).
11. R. Scholl and C. Seer, Ann. 394, 131, 175 (1912).
12. V. Weinmayr, F. S. Palmer, and A. A. Ebert, J. Am. Chem. Soc. 74, 4361 (1945).

NEW METHODS FOR SPONTANEOUS RESOLUTION OF RACEMIC MODIFICATIONS

Reported by Harry J. Neumiller November 21, 1952

I. INTRODUCTION

Spontaneous resolution may perhaps best be defined as any process of resolution in which either no optically active agent is introduced at all, or in which the amount of optically active agent introduced is extremely small in comparison with the amount of substance being resolved, the active agent serving only to initiate the process. The purpose of this report is to review briefly the earlier known methods of spontaneous resolution, and to discuss in some detail two recently discovered methods.

II. HISTORICAL

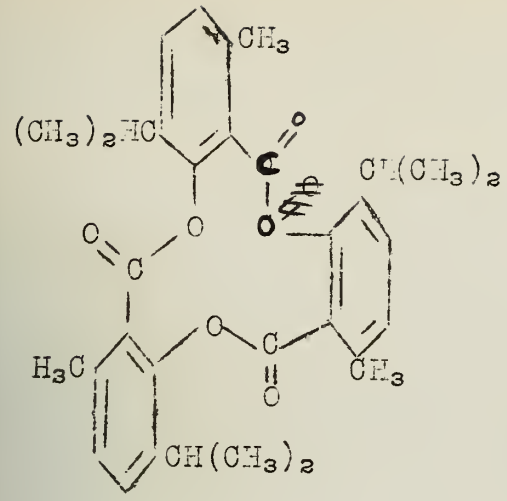
Pasteur[1,2] discovered in 1848, upon microscopic examination of sodium ammonium d,l-tartrate, that this substance consisted of two types of crystals which were non-superposable mirror images of each other. Upon separation of these two types of crystals by mechanical means, he obtained sodium ammonium (+)- and (-)-tartrates. In order to be resolved by this method, a racemic modification must crystallize or solidify as a conglomerate and give large crystals with well-formed hemihedral faces. Only a few substances which meet all of these requirements have been reported.[3]

A slightly more general procedure involves selective crystallization of one enantiomorph from a supersaturated solution of a racemic modification. Most of these procedures involve inoculation of the solution with a crystal of the enantiomorph to be crystallized. However, sodium ammonium (+)-tartrate has been precipitated from a solution of the enantiomorph by the addition of a crystal of (-)-asparagine,[4] the crystals of these two compounds being isomorphous. Resolution of atropine sulfate has been caused by microscopic crystals which were present in the atmosphere.[5]

III. NEW METHODS

A. Trithymotide

Tri-o-thymotide (I), a cyclic triester, has been shown to exist, due to hinderance between adjacent carbonyl and i-propyl groups, in a non-planar, "propellor"=like configuration,[6,7] in which the aromatic rings are arranged on the sides of a trigonal pyramid (Fig. 1). This gives rise to two enantiomorphous forms, which can be resolved by inoculating a solution of tri-o-thymotide with a crystal of the desired enantiomorph. However, since trithymotide possesses the property of crystallizing from a wide variety of solvents to give molecular complexes[6] of the form 2 $C_{33}H_{36}O_6 \cdot M$ (M≡1 molecule of solvent), selective crystallization yields not the pure enantiomorph, but a complex of enantiomorph and solvent.[8]



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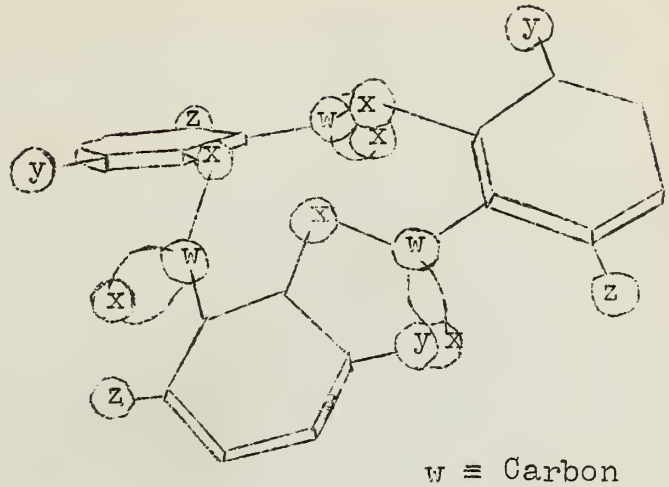


w ≡ Carbon

x ≡ Oxygen

y ≡ $-CH(CH_3)_2$

z ≡ $-CH_3$

Fig. 1

These complexes appear to be clathrate compounds.[9] Clathrate compounds are formed by the inclusion of one substance in cavities existing in the crystals of a second substance which, due to a more favorable potential energy value, does not crystallize in a form in which the molecules are packed in the closest possible manner. It might be expected that if an enatiomorphous substance were to crystallize in this way, the cavities would be dissymmetric, and that as a result one antipode of a solvent which was itself a racemic modification would be included in the cavities more readily than the other. Trithymotide has been shown to be capable of resolving a solvent in this manner, a partial resolution of 2-bromobutane having been attained in preliminary experiments.[8]

B. Urea Inclusion Compounds

It was discovered in 1940 that urea forms crystalline addition compounds with a large variety of straight-chain, saturated aliphatic hydrocarbons and their derivatives.[10,11] The combining ratios of moles of urea to moles of hydrocarbon in these compounds are not, in general, quotients of small intergers.[12] Recent investigation of the structure of the crystal lattice of the compounds has shown that the centers of the oxygen atoms of the urea molecules lie in the edges of regular hexagonal prisms, arranged in honey-comb fashion with the hydrocarbon chains situated along the axes of the prisms. The planes determined by the carbon and nitrogen atoms of the urea molecules lie in the faces of the prisms (Fig. 2).[12,13] This arrangement allows no centers of symmetry to exist in the crystals, and, as with crystalline quartz, the crystals have screw-axes as

their elements of symmetry. The formation of a right- or left-handed lattice is thereby allowed, giving rise to optical activity in the crystal. It has been shown to be possible, by selective crystallization, to cause only one of these lattices to form.[14]

If an inclusion compound were made from urea and a racemic modification, and if crystals of only one sense with respect to the screw-axis formed, the result would be two diastereomers. It would be expected that one of these would be more soluble than the other, and that a partial crystallization process would give more of the less soluble isomer. Decomposition of the crystals by redissolving them would give an optically active solution. In preliminary experiments, 2-chloroctane has been resolved in this manner. Although it has not yet been possible to achieve complete resolution by one crystallization, a preparation consisting of 95% (+)-2-chloroctane has been made by several repeated crystallizations.[14]

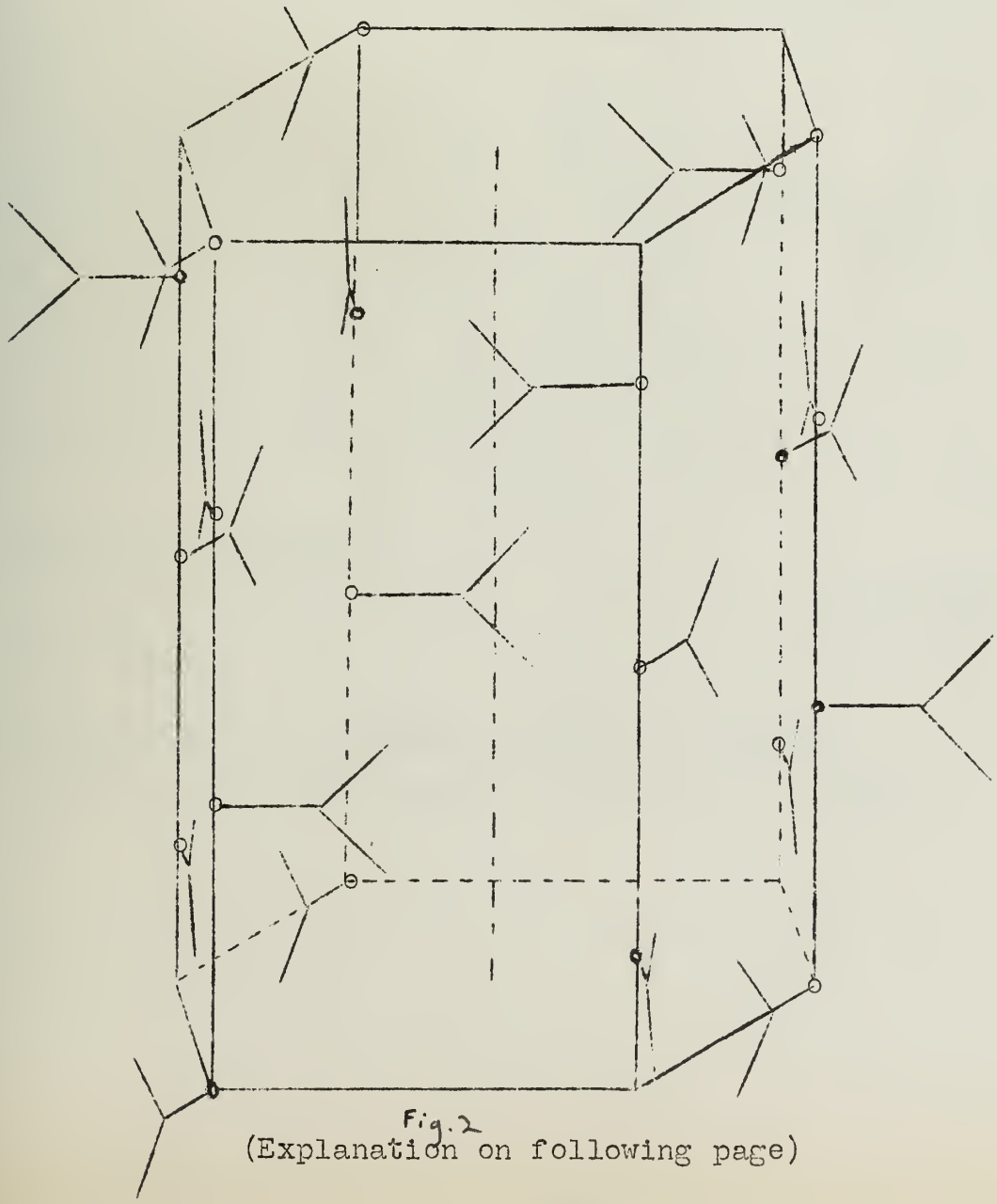
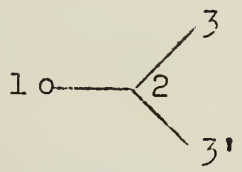


Fig. 2
(Explanation on following page)

— - — - — ≡ (Axis of cell and approximate position (of hydrocarbon chain.



≡ (Urea molecule [positions of atoms are: (1-oxygen, 2-carbon, 3,3'-NH_2]. Molecules (in which balls representing oxygen are (completely in black, together with por- (tion of hydrocarbon lying along indica- (ted axis, comprise a unit cell.

Fig. 2.
(Explanation)

BIBLIOGRAPHY

1. L. Pasteur, Ann. chim. et phys. [3], 24, 442 (1848); 28, 56 (1850)
2. L. Pasteur, "Researches on the Molecular Asymmetry of Natural Organic Products," Alembic Club Reprint No. 14, University of Chicago Press, Chicago, 1902.
3. F. Ebel, in K. Freudenberg, "Stereochemie," Franz Deutlicke, Leipzig and Vienna, 1933, p. 564.
4. I. Ostromisslensky, Ber. 41, 3035 (1908).
5. L. Anderson and D. J. Hill, J. Chem. Soc., 1928, 993.
6. W. Baker, B. Gilbert, and W. D. Ollis, J. Chem. Soc., 1952, 1443.
7. P. G. Edgerley and L. E. Sutton, J. Chem. Soc., 1951, 1069.
8. H. M. Powell, Nature, 170, 155 (1952).
9. H. M. Powell, J. Chem. Soc., 1948, 61.
10. F. Bengen and W. Schlenk Jr., Experientia 5, 200 (1949).
11. F. Bengen, Angew. Chem., 63, 207 (1951).
12. W. Schlenk Jr., Ann. 565, 204 (1949).
13. A. E. Smith, J. Chem. Phys. 18, 150 (1950).
14. W. Schlenk Jr., Experientia 8, 337 (1952).

ADDITIONAL REFERENCES

Clathrate Compounds:

15. D. E. Palin and H. M. Powell, J. Chem. Soc., 1947, 208; 1948, 571, 815.
16. H. M. Powell, J. Chem. Soc., 1950, 298, 300, 468.

General Review of Organic Inclusion Compounds:

17. W. Schlenk Jr., Fortschr.chem. Forsch. 2, 92 (1951).

THE REACTIONS OF HALOGEN (I) SALTS OF CARBOXYLIC ACIDS

Reported by George W. Parshall November 21, 1952

I. Preparation and Nature

The reaction of a metallic salt of a carboxylic acid with iodine, bromine or chlorine leads to the formation of the corresponding halogen (I) salt of the acid[1]. For example, the silver salt, which is usually the most convenient for preparative purposes[2], reacts with an equimolar quantity of iodine as in step A. However, if less than an equimolar quantity of iodine is used, the excess silver salt forms a complex with the iodine salt as in step B[3].

$$\text{(A)}\quad RCO_2Ag + I_2 \longrightarrow RCO_2I + AgI$$

$$\text{(B)}\quad RCO_2Ag + RCO_2I \longrightarrow (RCO_2)_2AgI$$

Although both the halogen salt and the complex are very sensitive to heat and moisture, Prevost has reported the isolation of the complex resulting from the reaction of equivalent quantities of iodine and silver benzoate[4]. Birckenbach and his co-workers have demonstrated the existence of iodine (I) acetate by treating cyclohexene with a silver-free solution of this salt and isolating the 1-acetoxy-2-iodocyclohexane which was formed[5].

The positive nature of the halogen in these salts was demonstrated by Beckenmiller and Hoffmann who found that a silver-free solution of bromine (I) butyrate has an oxidizing power equal to that of a bromine solution containing twice as much of the halogen[3].

II. Halogenation of Aromatic Compounds

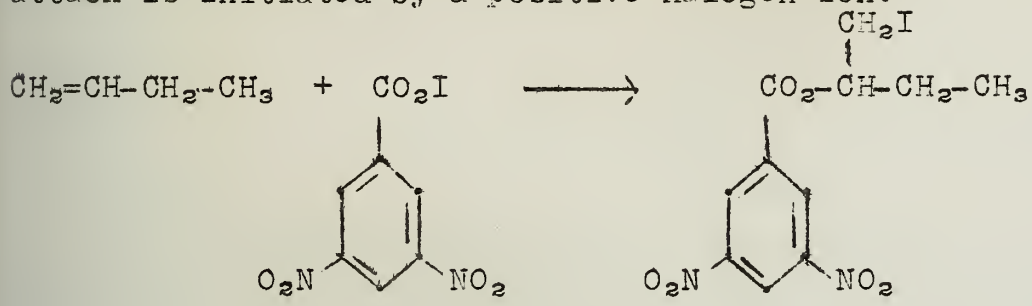
The iodine salts of strong carboxylic acids, such as trifluoroacetic acid, apparently dissociate to some extent to give carboxylate and iodonium ions. Since the latter are electrophilic, these salts may act as halogenating agents for aromatic compounds. Iodine trifluoroacetate has been found to give good yields of mono-iodinated products with a wide variety of aromatic compounds. Compounds containing electron-donating groups are iodinated almost exclusively at the <u>para</u> position, a fact which seems to confirm that this reaction proceeds by way of an ionic mechanism[6].

Although iodine trifluoroacetate has received the most intensive study, iodine acetate, bromine acetate and bromine trifluoroacetate have been shown to react similarly[7,8]. In the bromination of toluene with the latter reagent, the product may be either <u>p</u>-bromotoluene or benzyl bromide depending on the temperature at which the reaction is carried out[8].

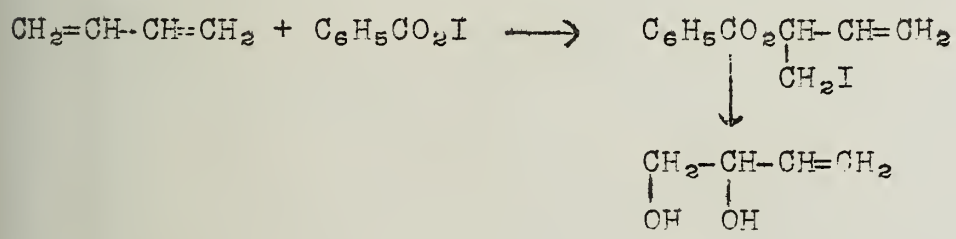
Many examples of self-halogenation of bromine salts of aromatic acids have been reported[7,9,10].

III. Addition to Olefinic Double Bonds

These halogen salts add to olefinic double bonds to form esters of α-halo alcohols as shown in the example below. This reaction proceeds so readily that it has been proposed as a means of preparing solid derivatives of simple olefins[11]. The orientation of the substituents is such as to suggest an ionic mechanism in which the attack is initiated by a positive halogen ion.

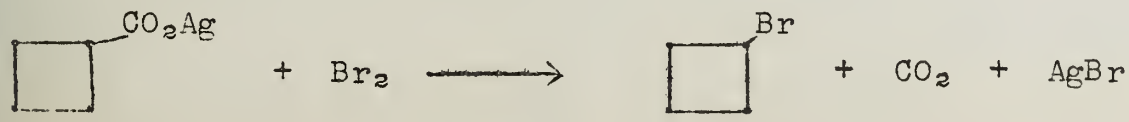


This reaction has been applied to a large number of ethylenic compounds[3,5,12,13] and Prevost has reported similar additions to acetylenic compounds[4]. The addition of iodine benzoate to butadiene was found to proceed in a 1,2 manner to give a product which could readily be hydrolyzed to 3,4-dihydroxy-1-butene[14].



IV. Decarboxylation

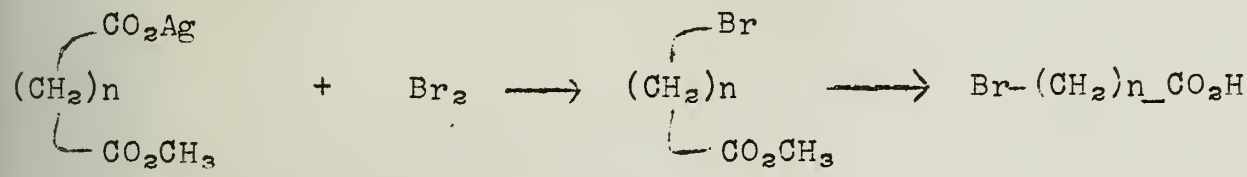
The best known reaction involving the halogen salts of carboxylic acids is the Hunsdiecker decarboxylation. In general this reaction is carried out by heating the silver salt of the acid with an equimolar quantity of bromine. As is shown in the case of cyclobutanecarboxylic acid, the carboxyl group is replaced by a bromine atom with the attendant formation of carbon dioxide and silver bromide[15]. However, if only an equivalent quantity of the halogen is used, the product is an ester as is shown with caproic acid[16,27].



$$2C_6H_{11}CO_2Ag + I_2 \longrightarrow C_5H_{11}CO_2C_5H_{11} + CO_2 + AgI$$

The mechanism of this reaction has been the subject of much controversy, especially with regard to the decarboxylation of aromatic acids. Although it is generally agreed that the halogen salts are intermediates, strong evidence has been presented for both the ionic and free radical mechanisms[7,9].

This decarboxylation has been reported to be stereochemically specific in the cases of (+) 2-phenylpropionic acid, (+) 2-benzylbutyric acid and (+) 2-ethylhexanoic acid[17,18,26]. Unfortunately, the products are usually racemized by the silver bromide which is formed in the reaction mixture.



One of the most common uses of this reaction is for the preparation of ω-bromo acids from the mono-esters of dicarboxylic acids[19,20]. It has also proven very useful for introducing chlorine, bromine or iodine into perfluoroalkyl compounds[21-25].

Bibliography

1. J. Kleinberg, Chem. Rev., 40, 381 (1947).
2. R. N. Haszeldine, J. Chem. Soc., 584 (1951).
3. W. Bockemüller and F. W. Hoffmann, Ann., 519, 165 (1935).
4. C. Prevost, Compt. rend., 196, 1129 (1933).
5. L. Birckenbach, J. Goubeau and E. Berninger, Ber., 65, 1339 (1932).
6. R. N. Haszeldine and A. G. Sharpe, J. Chem. Soc., 993 (1952).
7. W. G. Dauben and H. Tilles, J. Am. Chem. Soc., 72, 3185 (1950).
8. A. L. Henne and W. F. Zimmer, ibid., 73, 1362 (1951).
9. R. A. Barnes and R. J. Prochaska, ibid., 72, 3188 (1950).
10. K. Birnbaum and H. Reinherz, Ber., 15, 456 (1882).
11. B. I. Halpe rin, H. B. Donahoe, J. Kleinberg and C. A. VanderWerf, J. Org. Chem., 17, 623 (1952).
12. C. Prevost, Compt. rend., 197, 1661 (1934).
13. D. C. Abbott and C. L. Arcus, J. Chem. Soc., 1515 (1952).
14. C. Prevost and R. Lutz, Compt. rend., 198, 2264 (1934).
15. J. Cason and R. L. Way, J. Org. Chem., 14, 31 (1949).
16. A. Simonini, Monatsh., 13, 320 (1892).
17. D. C. Abbott and C. L. Arcus, J. Chem. Soc., 3195 (1952).
18. C. L. Arcus, A. Campbell and J. Kenyon, ibid., 1510 (1949).
19. A. Luttringhaus and D. Schade, Ber., 74B, 1565 (1941).
20. H. Hunsdiecker and C. Hunsdiecker, Ber., 75B, 291 (1942).
21. R. N. Haszeldine, J. Chem. Soc., 3490 (1952).
22. M. Hauptschein and A. V. Grosse, J. Am. Chem. Soc., 73, 2461 (1951).
23. M. Hauptschein, et al., ibid., 74, 848 (1952).
24. M. Hauptschein, et al., ibid., 74, 1347 (1952).
25. M. Hauptschein, et al., ibid., 74, 849 (1952).
26. F. Bell and I. F. B. Smyth, J. Chem. Soc., 2372 (1949).
27. J. W. H. Oldham, ibid., 100 (1950).

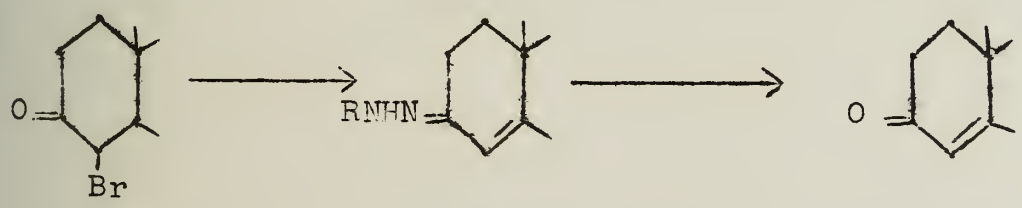
THE REACTION OF α-HALOKETONES WITH DINITROPHENYLHYDRAZINE

Reported by Fabian T. Fang December 5, 1952

Introduction

α-Haloketones in general present some interesting features in their behavior toward the usual carbonyl reagents. Hantzsch and Wild[1] reported in 1896 that compounds of the type R_1-CHX-CO-R_2 formed osazones and 1,2-dioximes with 1-3 moles of phenylhydrazine and hydroxylamine, respectively. Curtin and Tristram[2] furnished evidence in favo of a tetrahydropyridazine structure for the product of the reaction between α-haloacetophenones and phenylhydrazine. With hydroxylamine, α-bromoacetophenone is reported to form the dioxime of phenylglyoxal[3]. An unsuccessful attempt to prepare the carboxyphenylhydrazone of 2-chlorocyclohexanone has been recorded[4] and this is in agreement with the isolation of a dinitrophenylosazone[5] and of a 1,2-dioxime[6] on treatment of the same ketone with the corresponding carbonyl reagent.

In 1948, Mattox and Kendall[7] recorded in a preliminary communication the interesting observation that when certain hormone intermediates containing the 3-keto-4-bromo grouping (I) were treated in acetic acid solution with 1.2 moles of dinitrophenylhydrazine in the absence of molecular oxygen with or without the addition of sodium acetate, the dinitrophenylhydrazone (II) of the corresponding Δ^4-3-ketosteroid was obtained in excellent yield. Furthermore, on cleavage with pyruvic acid in the presence of hydrogen bromide, the unsaturated ketone (III) could be regenerated almost quantitatively.



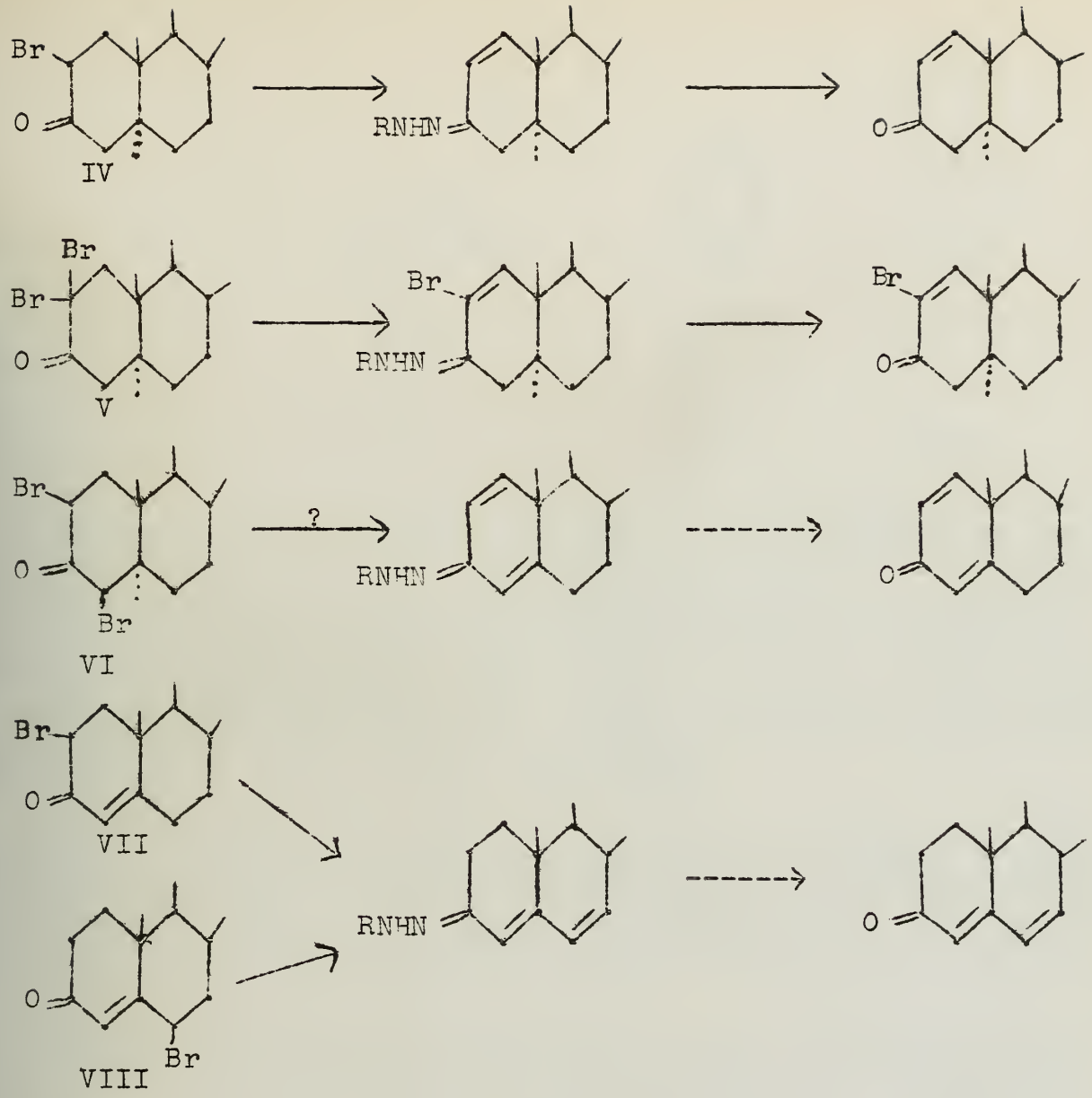
I II III

R = 2,4-$(NO_2)_2C_6H_3$-

Further studies[8,9,10] have been prompted on the course of this smooth and useful dehydrohalogenation which is sometimes known as the Mattox-Kendall reaction.

Scope and Limitation

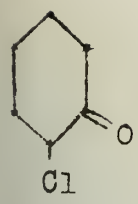
Djerassi[8] extended the reaction to other 3-keto-α-bromosteroids. He found that the reaction of the steroidal bromoketone with 1.0-1.1 moles of dinitrophenylhydrazine was completed after heating for three to five minutes. In addition to the 4-bromoketones (I), the method is applicable to the dehydrobromination of 2-bromo- (IV) and 2,2-dibromo-3-keto<u>allo</u>steroids (V) as well as 2-bromo- (VII) and 6-bromo-Δ^4-3-ketosteroids (VIII). The last two compounds both yield the hydrazone of the $\Delta^{4,6}$-dien-3-one. The results are not conclusive in the case of 2,4-dibromo-3-keto<u>allo</u>steroids (VI).



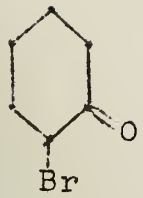
The regeneration of the unsaturated carbonyl compounds from the dinitrophenylhydrazones was found to be feasible from a preparative standpoint only in the case of the Δ^1- and Δ^4-3-ketones, thus imposing somewhat of a limitation on this reaction.

Phenylhydrazine, α-(2,4-dinitrophenyl)-α-methylhydrazine, hydroxylamine and semicarbazide produced essentially the same results as dinitrophenylhydrazine. Dinitrophenylhydrazine surpasses all other reagents because of the ease with which the dinitrophenylhydrazones crystallize in the steroid series.

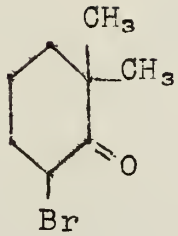
Ramirez and Kirby[10] investigated this dehydrohalogenation procedure with simple α-haloketones of varied structures other than steroids. The α-halo dinitrophenylhydrazones of the following ketones were prepared in good yields by means of an aqueous methanolic solution of 2,4-dinitrophenylhydrazine sulfate containing excess sulfuric acid (Brady's reagent[11]).



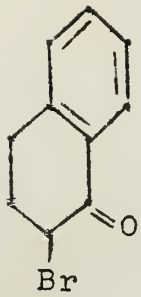
IX



X



XI



XII

XIII

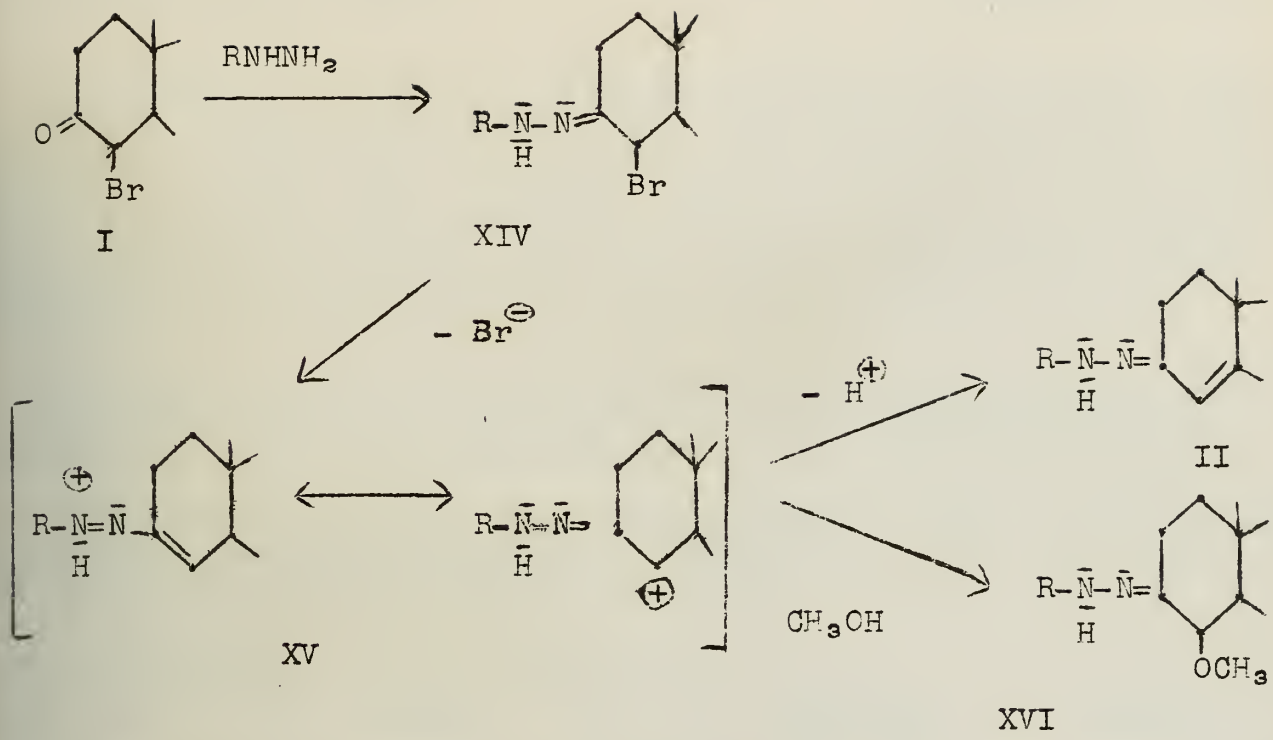
In general these hydrazones proved to be quite stable when pure or in solutions of non-hydroxylic solvents. When solutions of the α-halo hydrazones of IX, X or XI in acetic acid were kept at their boiling points for five minutes, smooth dehydrohalogenation took place with formation of the corresponding α,β-unsaturated dinitrophenylhydrazones. The same results were obtained on similar treatment of solutions of the α-haloketones IX, X or XI in acetic acid with one mole of 2,4-dinitrophenylhydrazine; the products isolated were the unsaturated hydrazones. The elimination of hydrogen halide appeared to proceed slowly if at all at room temperature.

In the two cases (XII and XIII) in which an aromatic ring was conjugated to the dinitrophenylhydrazone group, no hydrogen bromide was eliminated under conditions comparable to or even more drastic than those described above. As shown by the behavior of XI, the degree of substitution on a position adjacent to the hydrazone group seems to play no important role in the elimination.

The lability of the α-halogen atoms in the hydrazones of IX, X and XI is apparent in their behavior toward methanol. In this solvent formation of the corresponding α-methoxy hydrazone was essentially complete on warming for a few minutes. The same treatment applied to 2-bromo-1-tetralone (XII) also led to an α-methoxy hydraxone. The α-halo hydrazones and the α-methoxy hydrazones obtained from IX, X and XI were all converted into the corresponding osazones by an excess of Brady's reagent.

Mechanism

The most probable mechanism of the reaction of α-haloketones with dinitrophenylhydrazine is that suggested by Mattox and Kendall[9].



The α-bromo hydrazone XIV is initially formed. The loss of a bromide ion by solvolysis leads to the resonance-stabilized ion XV which then reacts either through loss of a proton and formation of a double bond to give the unsaturated hydrazone II or through the addition of a negative group to give the substituent XVI.

The observations of Ramirez and Kirby[10] are consistent with the view that in this reaction the formation of the α-halo hydrazone precedes the dehydrohalogenation step.

BIBLIOGRAPHY

1. Hantzsch and Wild, Ann., 289, 285 (1896).
2. Curtin and Tristram, J. Am. Chem. Soc., 72, 5238 (1950).
3. Scholl and Matthaiopoulos, Ber., 29, 1550 (1896).
4. Murphy and Jenkins, J. Am. Pharm. Assoc., 32, 83 (1943).
5. Loftfield, J. Am. Chem. Soc., 73, 4707 (1951).
6. Tokura and Oda, Bull. Inst. Phys. Chem. Research (Tokyo), 22, 850 (1943).
7. Mattox and Kendall, J. Am. Chem. Soc., 70, 882 (1948).
8. Djerassi, ibid., 71, 1003 (1949).
9. Mattox and Kendall, ibid., 72, 2290 (1950).
10. Ramirez and Kirby, ibid., 74, 4331 (1952).
11. Brady, J. Chem. Soc., 757 (1931).

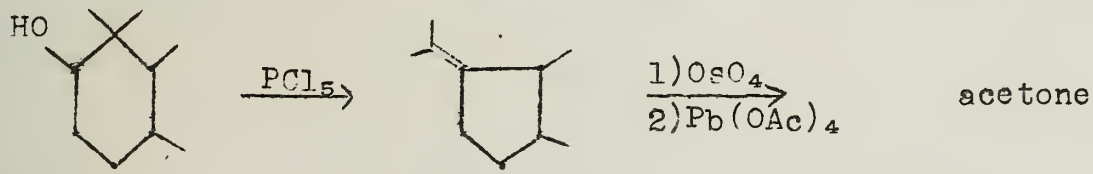
LANOSTADIENOL

Reported by David M. Locke December 5, 1952

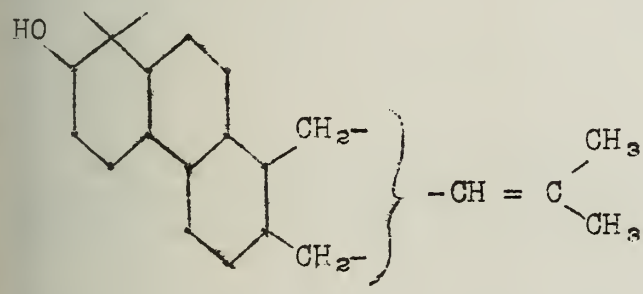
Lanostadienol is one of a group of tetracyclic triterpenes known as "isocholesterol" found in wool fat[1] and in the mother liquor from the preparation of ergosterol from yeast[2]. Its structure has been of considerable interest since it exhibits reactions characteristic of both sterols and amyrins. The molecular formula is found to be $C_{30}H_{50}O$; the compound contains two double bonds, one readily hydrogenated and one resistant to hydrogenation, four rings, and a secondary hydroxyl group[1,2].

The most available point of attack for degradation studies is the reactive double bond. By ozonolysis and osmium tetroxide-hydrogen peroxide this double bond may be placed in the $-CH=C(CH_3)_2$ moiety[3,4].

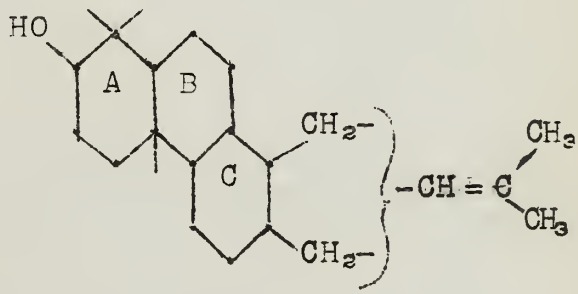
The secondary hydroxyl group also provides a point of ready attack. Phosphorus pentachloride leads to a rearrangement exactly analagous to that in the pentacyclic triterpene series[5].



Dehydrogenation of lanostadienol or of lanostene (side-chain hydrogenated and hydroxyl group reduced) with selenium yields 1,2,8-trimethylphenanthrene[6,7,8]. Thus structure I is indicated as a partial formula for lanostadienol.



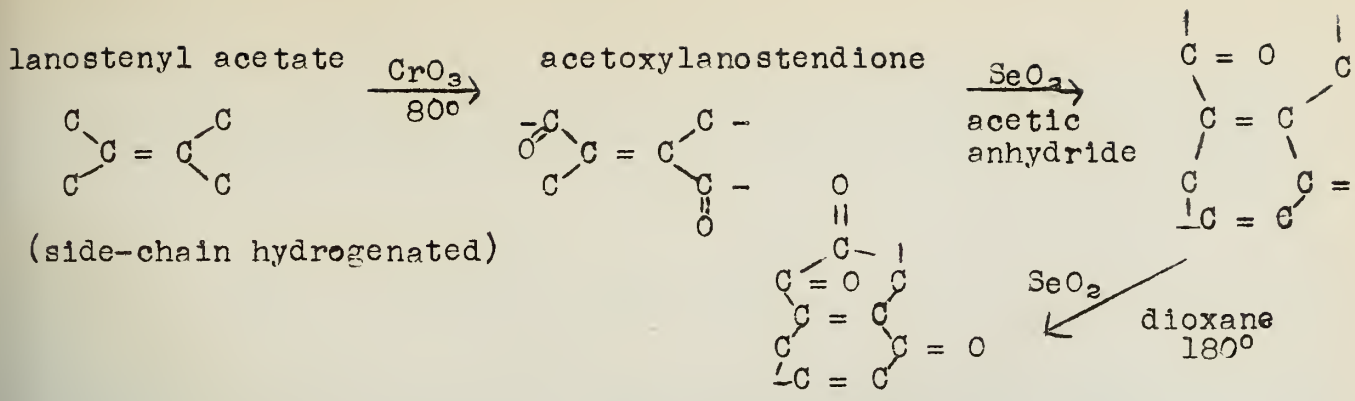
I



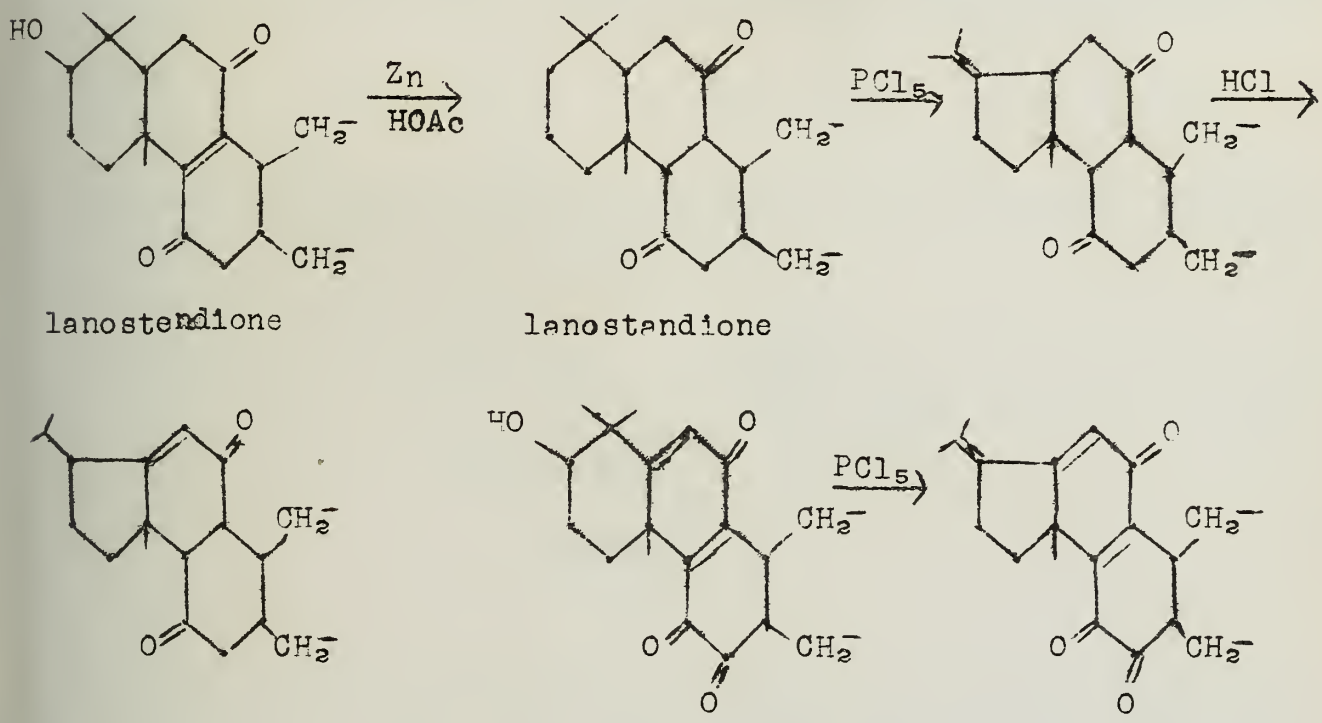
II

In addition an angular methyl group might now be tentatively placed at the A:B ring juncture since one appears in this position in the other di- and triterpenes (structure II).

Infrared evidence suggests that the nuclear double bond is tetrasubstituted, and the following sequence of reactions suggests that it occurs at a ring juncture[9].

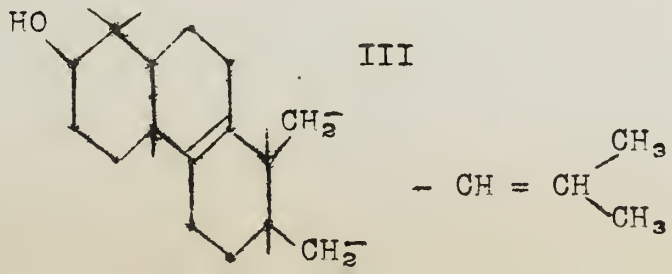


It may be shown that the particular ring juncture at which the double bond occurs is the B:C ring juncture[7,10].



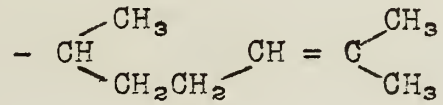
In each case the extension of the conjugated system by the introduction of the additional double bond in ring A indicates that the original point of unsaturation did indeed lie at the B:C ring juncture.

It should be noted that there is no extension of the conjugated system to the D ring. Furthermore, there is no evidence for any unsaturation extending to the carbons at the C:D ring juncture[11,12,7]. This evidence together with the dehydrogenation to 1,2,8-trimethylphenanthrene suggests two angular methyl groups at this ring juncture. The partial formula may now be represented by III.



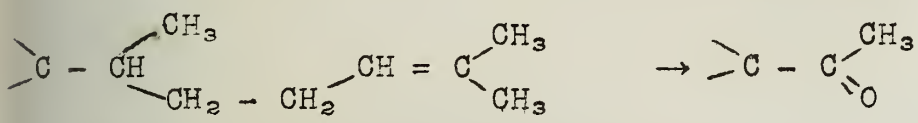
III

Oxidation of lanostenyl acetate (and of diketolanostenyl acetate) yields a small amount of acetone and 6-methylheptanone-2, identified as the 2,4-dinitrophenylhydrazones and semicarbazones[13,14]. This indicates that the side chain may be represented by the partial formula IV.

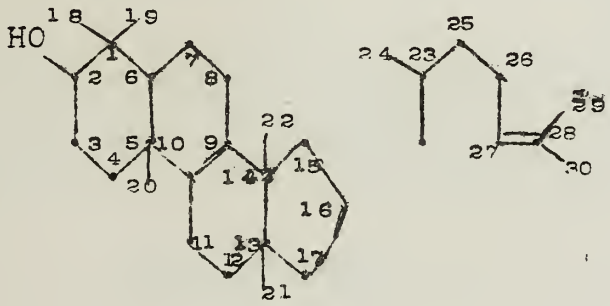
IV 

A modified Barbier-Wieland degradation of the side chain has also been accomplished, indicating the same partial formula[8,15-18].

Direct evidence for the size of ring D has been obtained from the tetracyclic degradation product from the Barbier-Wieland series[18,19].



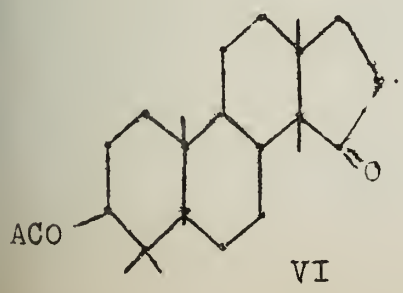
Infrared indicates a ketone function in a five-membered ring and thus suggests formula V for lanostadionol.



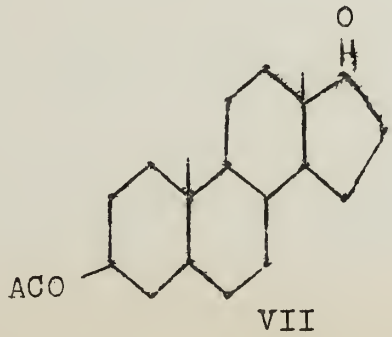
V

The only remaining uncertainty is the point of attachment of the side chain to the D ring. Two recent papers which discuss this point have appeared.

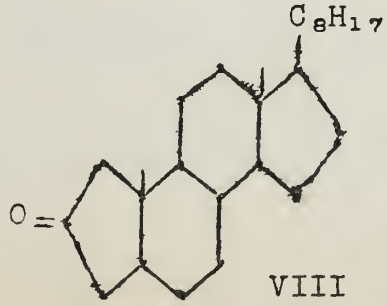
D. H. R. Barton and coworkers[20] have obtained a ring D ketone (VI) to which they have assigned the 15-keto structure rather than the 16-keto (not considering the 17-keto because it violates the isoprene rule) by comparing it with two other ketones, 3β-acetoxyandrostanone (VII) and A-norcholestanone (VIII).



VI



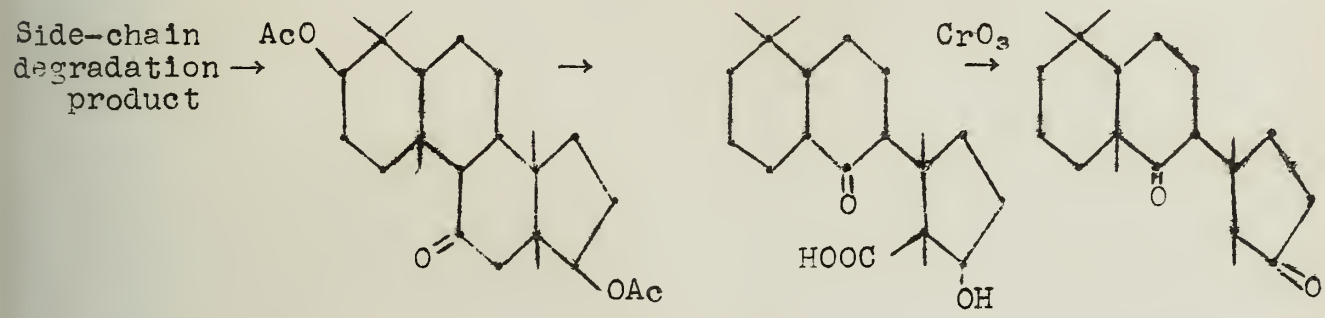
VII



VIII

VI showed significant steric hindrance being 1000 times slower than VII or VIII in reaction with 2,4-dinitrophenylhydrazine. In quantitative bromination VI and VII took up ca. 2 moles of bromine while VIII took up more than 3 under the same conditions. The intensity of the infrared absorption band at 1410 cm.$^{-1}$ (indicating methylene alpha to a carbonyl in a five-membered ring) was twice as large for VIII as for the other two ketones. This evidence indicates that of the structures 15-keto or 16-keto the former is far more likely for VI.

Swiss workers[21] have indicated in an "addendum in proof" to a recent article that they have carried out the following series of reactions:



The decarboxylation attending the oxidation indicates that a β-keto acid is produced, and this could occur only if the side chain had been attached at carbon 17. This work, however, can not be properly evaluated until the experimental details are published.

Bibliography

1. A. Windaus and R. Tschesche, Z. physiol. Chem., 190, 51 (1930).
2. H. Wieland, H. Posedach, and A. Ballauf, Ann., 529, 68 (1937).
3. H. Wieland and W. Benend, Z. physiol. Chem., 274, 215 (1942).
4. H. Wieland and E. Joost, Ann., 546, 103 (1941).
5. L. Ruzicka, M. Montavon, and O. Jeger, Helv. Chim. Acta, 31, 818 (1948).
6. H. Schulze, Z. physiol. Chem., 238, 35 (1936).
7. D. H. R. Barton, J. Fawcett, and B. R. Thomas, J. Chem. Soc., 3147 (1951).
8. W. Voser, M. Mijovic, O. Jege r, and L. Ruzicka, Helv. Chim. Acta, 34, 1585 (1951).
9. W. Voser, M. Montavon, Hs. Günthard, O. Jeger, and L. Ruzicka, ibid 33, 1893 (1950).
10. J. Cavalla, J. McGhie, and M. Pradhan, J. Chem. Soc., 3142 (1951).
11. R. Marker, E. Wittle, and L. Mixon, J. Am. Chem. Soc., 59, 1368 (1937).
12. L. Ruzicka, Ed. Rey, and A. Muhr, Helv. Chim. Acta, 27, 472 (1944).
13. C. Barnes, D. Barton, J. Fawcett, S. Knight, J. McGhie, M. Pradhan, and B. Thomas, Chem. and Ind., 1067 (1951).
14. C. Barnes, D. Barton, J. Fawcett, and B. Thomas, J. Chem. Soc., 2339 (1952).
15. J. McGhie, M. Pradhan, J. Cavalla, and S. Knight, Chem. and Ind., 1165 (1951).

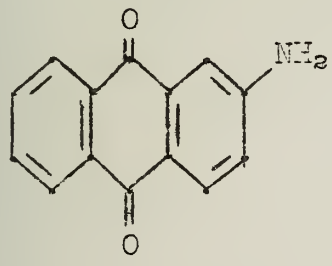
16. R. Curtis and H. Silberman, J. Chem. Soc., 1187 (1952).
17. W. Voser, O. Jeger, and L. Ruzicka, Helv. Chim. Acta, 35, 497 (1952).
18. W. Voser, O. Jeger, and L. Ruzicka, ibid., 35, 503 (1952).
19. W. Voser, Hs. Gunthard, O. Jeger, and L. Ruzicka, ibid, 35, 60 (1952).
20. C. Barnes, D. Barton, A. Cole, J. Fawcett, and B. Thomas, Chem. and Ind., 426 (1952).
21. W. Voser, Hs. Gunthard, H. Heusser, O. Jeger, and L. Ruzicka, Helv Chim. Acta, 35, 2065 (1952).

RECENT STUDIES IN THE CHEMISTRY OF INDANTHRONES

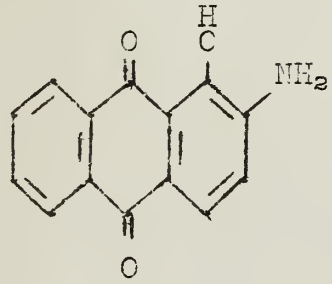
Reported by William H. Lowden December 5, 1952

Owing to their utility as vat dyes, the chemistry of the indanthrones has been the subject of considerable research. The first of these dyes, Indanthrene Blue R, the trivial name for indanthrone, was investigated in 1901.

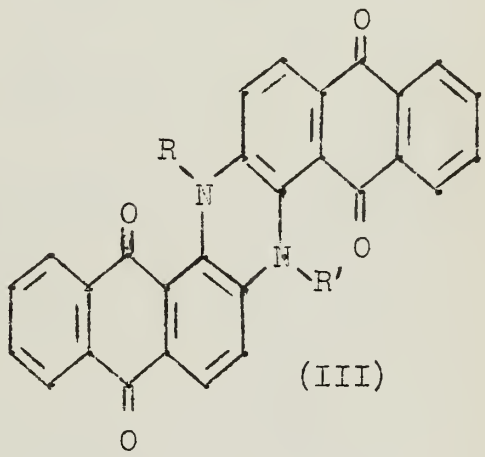
The synthesis of indanthrone (III, R=R'=H) by heating 2-aminoanthraquinone (I) with potassium hydroxide has initiated considerable controversy concerning the mechanism of the reaction.[1] Although the originally assigned structure has been accepted, the postulated mechanism has long since been proved erroneous.[3,4] The formation of the intermediate compound (II) was disproved and a new mechanism which involved sym-di-2-anthraquinonylhydrazine (IV) as a precursor to indanthrone was postulated.[4] However, it was soon noticed that this interpretation could be valid only in acidic media.[5] It was also suggested that the enolic form of compound (I) ought to combine with another molecule of itself yielding 2-amino-1:2'-dianthraquinonyamine (V, R=R'=H).[4] The enolic form of this adduct could then form indanthrone by cyclization and oxidation. This imine addition proces proved quite popular and several investigators suggested slight



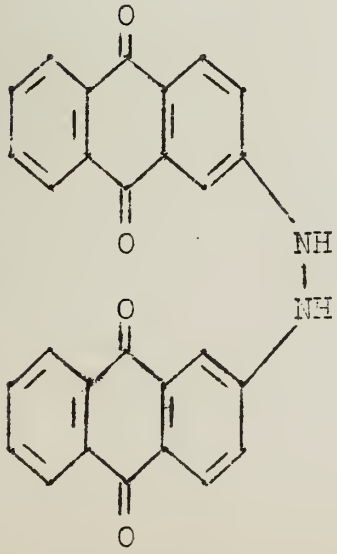
(I)



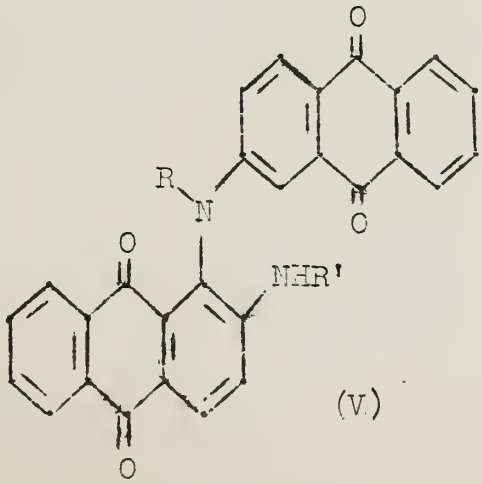
(II)



(III)

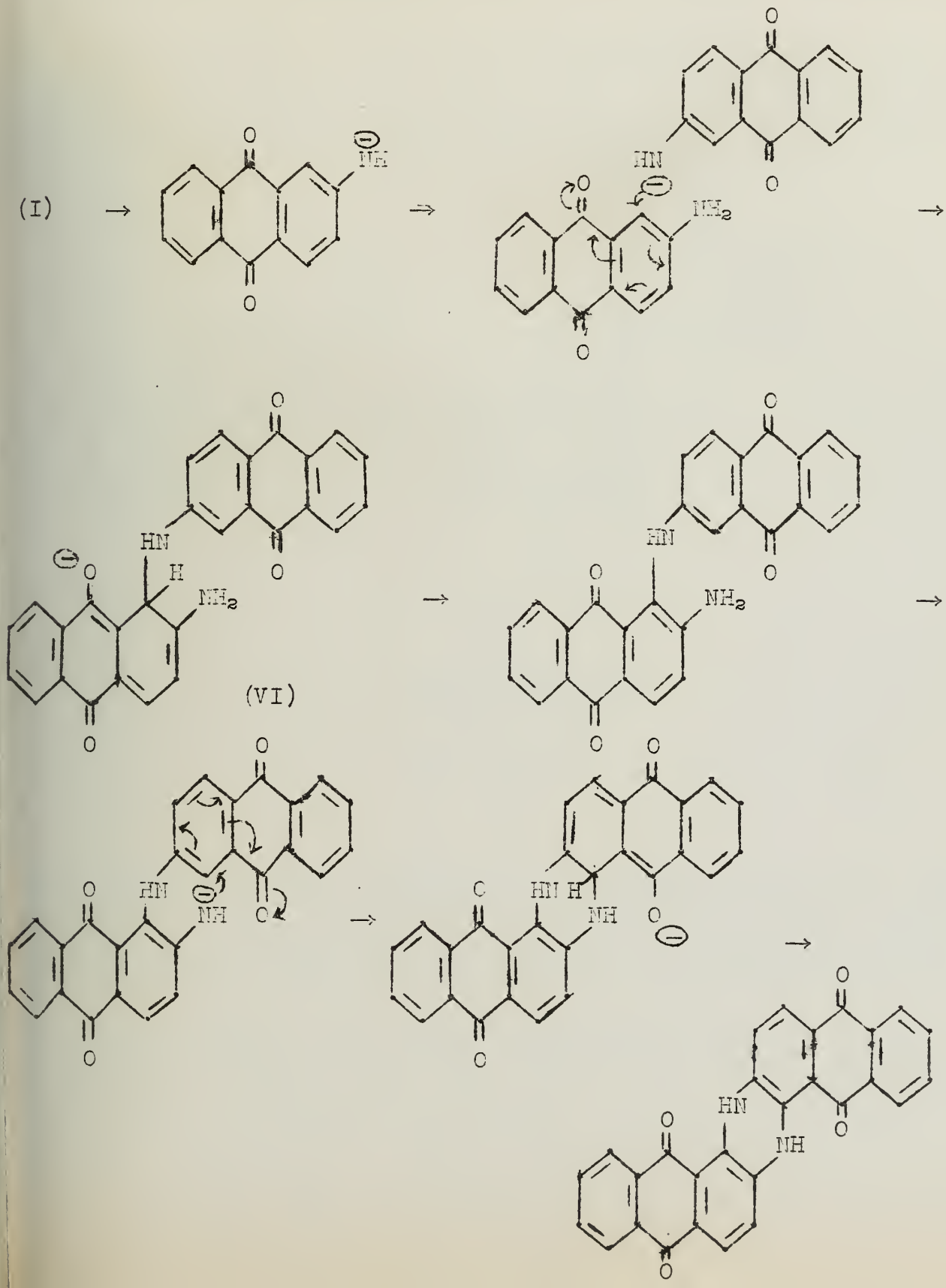


(IV)



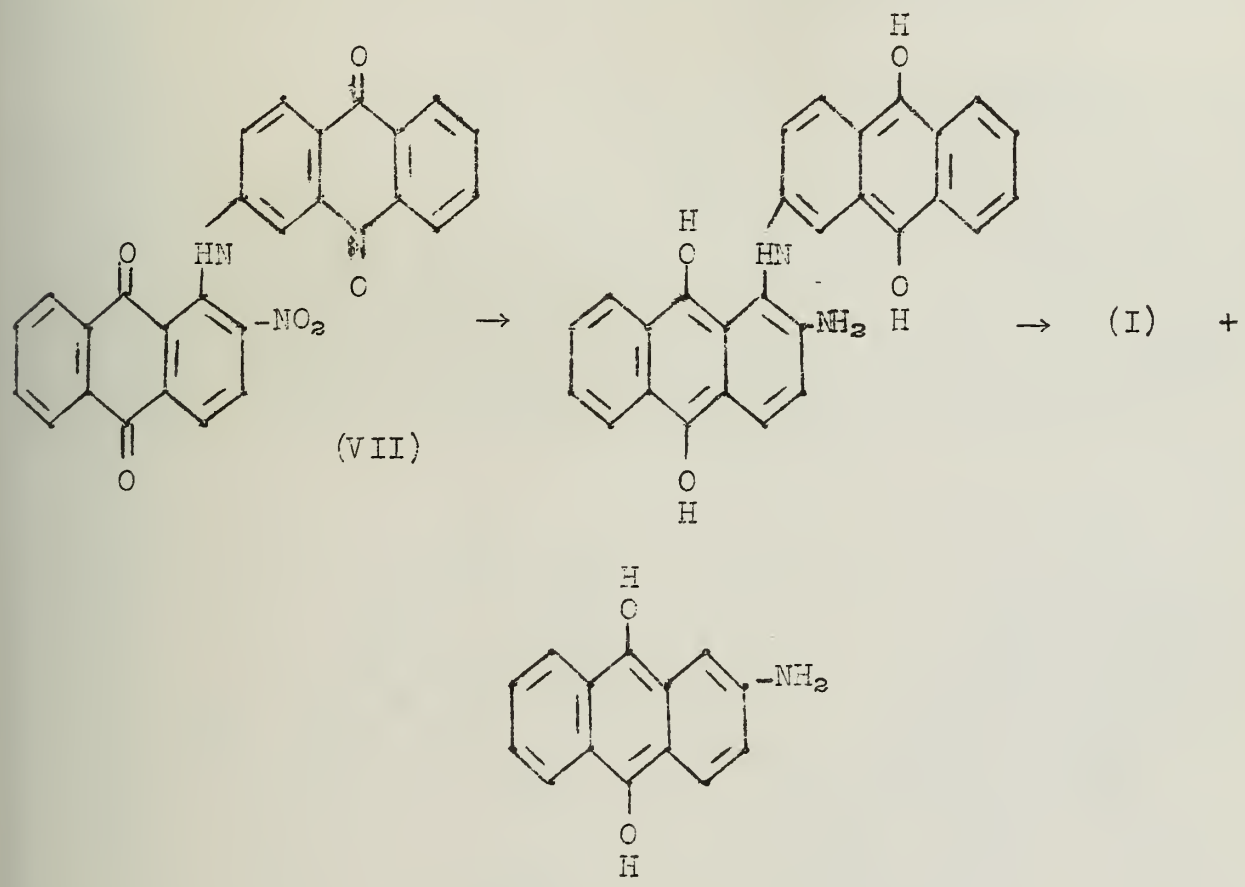
(V)

modifications.[6,7,9] Two other view-points were also proposed, a quinonoid-ion-radical hypothesis[10] and a nuclear hydrogen substitution by the anion of (I).[11] Recently a series of papers has appeared in which this problem has been more thoroughly investigated.[12-18]



2-Amino-1:2'-dianthraquinonylamine was prepared and cyclized to indanthrone in acid, neutral and alkaline media.[12] Indanthrone results when the free amine is heated at 290°, or warmed in glacial acetic acid. Boiling pyridine does not cyclize the free amine, although potassium hydroxide in cold pyridine does. The N-methyl derivatives, however, require an alkaline medium.

Upon reduction of 2-nitro-1:2'-dianthraquinonylamine (VII) with alkaline dithionite, 2-aminoanthraquinone and 2-aminoanthraquinol result. This observation is interpreted by the postulation of the elimination of the 2-anthraquinonylamine-substituent from the 1-position of the 2-aminoanthraquinol nucleus.



The instability of the intermediate is evidence in support of the reduced form (VI) of (V, R=R'=H) as an intermediate in the formation of indanthrone. It is evidence for the weakness of the bond linking the secondary nitrogen to the 1-position of the aminated nucleus. It also suggests that the bond formation is a reversible process.

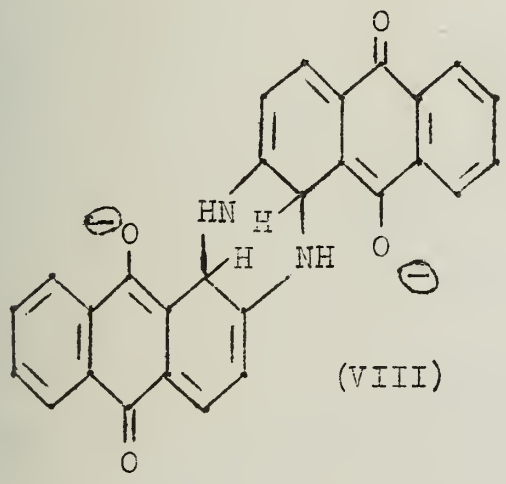
Enolization of (V) would be a plausible mechanism for the ring closure to indanthrone; however, observations with the N-methyl derivative (V, R=Me, R'=H), which cannot occur in an analogous enolic form, tend to discount this mechanism. Ring closure occurred when this compound was heated with potassium hydroxide in pyridine, yielding (III, R=Me, R'=H). However, with the dimethyl derivative (V, R=R'=Me) hot methanolic potassium hydroxide was necessary to form (III, R=R'=Me). These data permit the conclusion that enolization is not an essential step in the linking of the nitrogen to the nucleus.

It has been concluded that the same line of reasoning is valid in the union of two molecules of anthraquinone.[12]

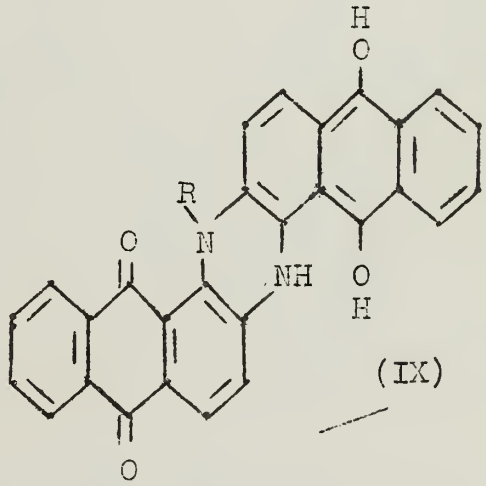
The substituting ability of 2-aminoanthraquinone is predictable on the basis of the rule that only the anions of the weakest bases are able to replace nuclear hydrogen in aromatic nitro or carbonyl compounds. Evidence in support of this rule is the fact that 2-amin anthraquinone will condense with nitrobenzene in the presence of strong base to give 2-p-nitroanilinoanthraquinone.

A hydrogen atom adjacent to a carbonyl group can be replaced by an amino group without great difficulty. This is illustrated by the fact that 2-aminoanthraquinone will undergo substitution at the 1-position by hydroxyl and anilinium ions.[8,9]

It has been suggested that the stability of indanthrone (or som intermediate) is the reason why other products do not occur in abundance from the alkali fusion of 2-aminoanthraquinone.[12] It has long been recognized that the unusual stability of indanthrone was due to the four carbonyl groups.[2] With this stability factor in mind, it i reasonable to assume that the ease of formation of indanthrone may b determined by the ease of formation of (VIII). As a result of the methanol-potassium hydroxide color test, it is quite possible that the methyl derivatives of (V) pass through a dihydro intermediate (IX, R=Me). Powdered sodium hydroxide converted (V, R=H) to (IX, R=H), which could be explained by the shift of two protons.

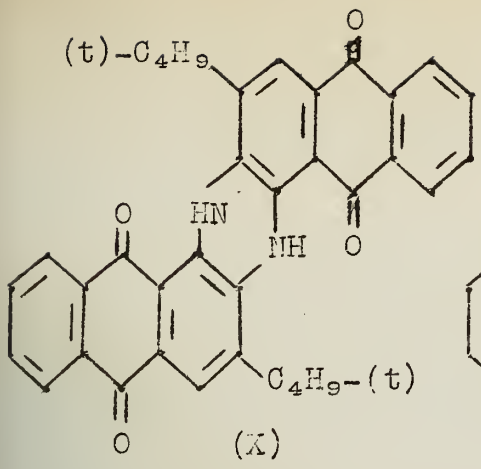


(VIII)

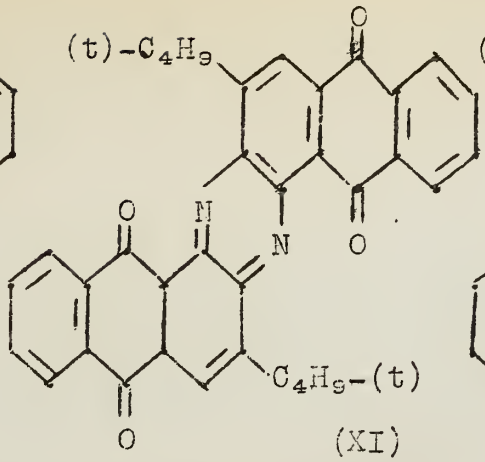


(IX)

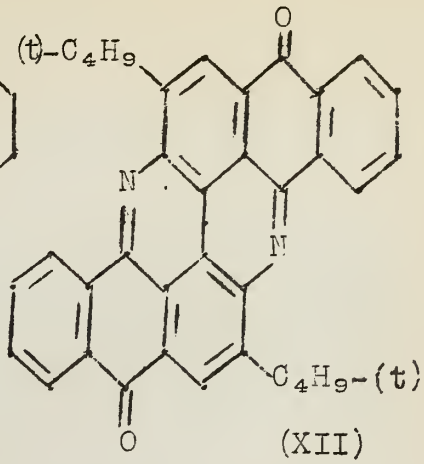
An interesting reaction takes place when 2-amino-3-t-butyl-anthraquinone is heated at 300° with potassium hydroxide. No 3,3'-di-t-butylindanthrone (X) or the corresponding azine (XI) is formed. Instead, a 65% yield of 3,3'-di-t-butylflavanthrone (XII) is realized. Even at 220° no (X) or (XI) is formed.



(X)

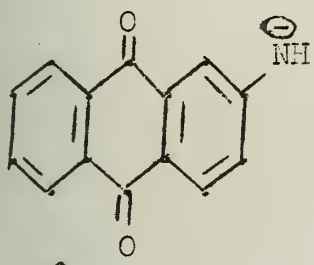


(XI)



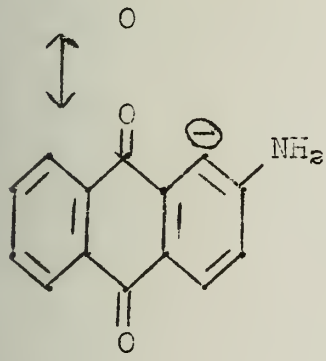
(XII)

It was noticed that flavanthrone was also a product of the alkali fusion of 2-aminoanthraquinone. Two inadequate mechanisms were postulated for the formation of this product.[9,10] The more recent investigators have accounted for its formation in a similar manner as the indanthrone derivative.[16]

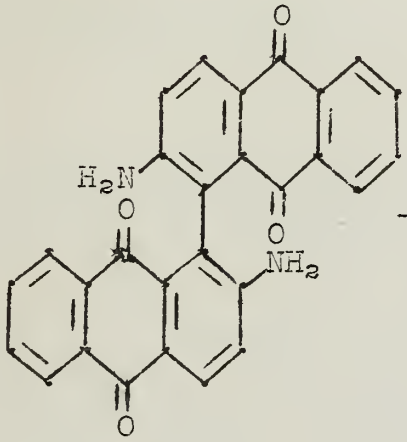


$\xrightarrow{(I)}$ (V, R=R'=H) $\rightarrow$ (III, R=R'=H)

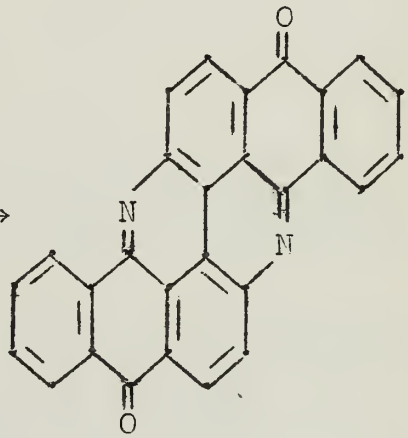
indanthrone



$\xrightarrow{(I)}$



$\rightarrow$



flavanthrone

Bibliography

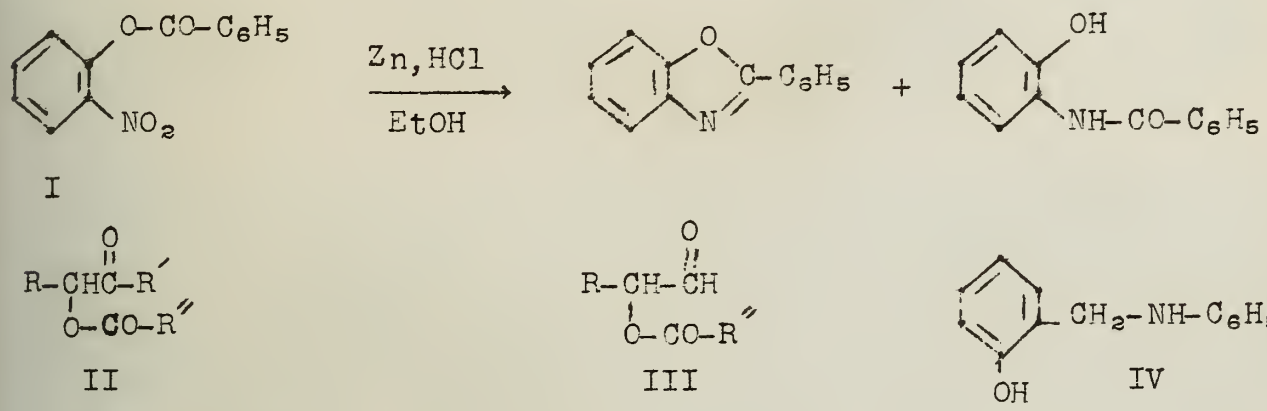
1. Bohn, G. P. 129,845. Feb. 6, 1901.
2. Scholl, Ber., 36, 3410 (1903).
3. Scholl, Berblinger and Mansfield, Ber., 40, 320, 1691 (1907).
4. Scholl and Eberl, Monatsh., 32, 1035 (1911).
5. Kopetschni, Chem. Zentr., II, 2506 (1924).
6. Barnett, "Anthracene and Anthraquinone," London, 1921.
7. Maki, J. Soc. Chem. Ind. Japan, Suppl., 32, 303 (1929).
8. Maki, ibid., 37, 748 (1934).
9. Tanaka, J. Chem. Soc., Japan, 56, 192 (1935).
10. Schwenk, Chem.-Ztg., 52, 45 (1928).
11. Bradley and Robinson, J. Chem. Soc., 1254 (1932).
12. Bradley and Leete, ibid., 2129 (1951).
13. Bradley and Leete, ibid., 2147 (1951).
14. Bradley, Leete and Stephens, ibid., 2158 (1951).
15. Bradley, Leete and Stephens, ibid., 2163 (1951).
16. Bradley and Nursten, ibid., 2170 (1951).
17. Bradley and Nursten, ibid., 2177 (1951).
18. Bradley and Nursten, ibid., 3027 (1952).

ACYL O ⇌ N MIGRATIONS

Reported by Howard J. Burke December 12, 1952

INTRODUCTION

The first recorded O to N acyl migration seems to be that noted in 1883 during the reduction of o-nitrophenyl benzoate (I).[1] European workers, until recently, have concerned themselves with analogous migrations which occur during the formation of phenylhydrazones of α-acyloxyketones (II) and α-acyloxyaldehydes (III),[2] and during the formation of o-hydroxybenzyl anilides (IV).[3]

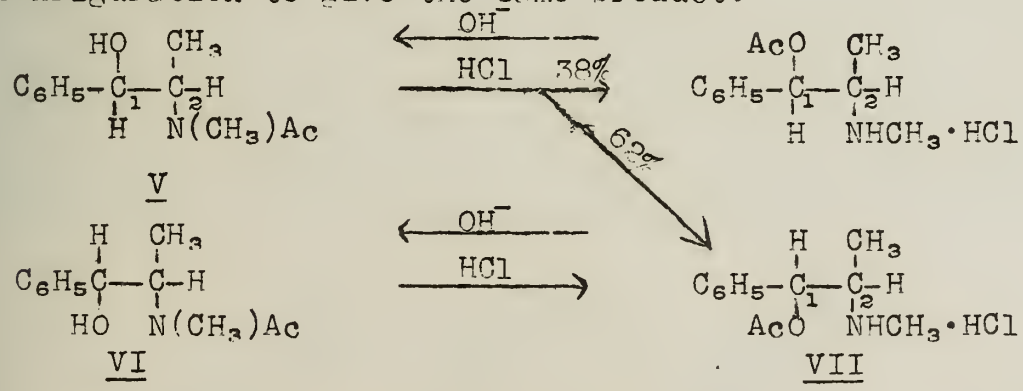


Since, however, these migrations are not reversible by a shift in the pH, we shall not discuss them further.

REVERSIBLE MIGRATIONS

Reversible acyl migrations between O and N were noted in the β-aminopropanol series in 1935.[4] The subject was pursued somewhat further until the outbreak of war,[5-7] but really useful applications of such migrations were not brought out until later.

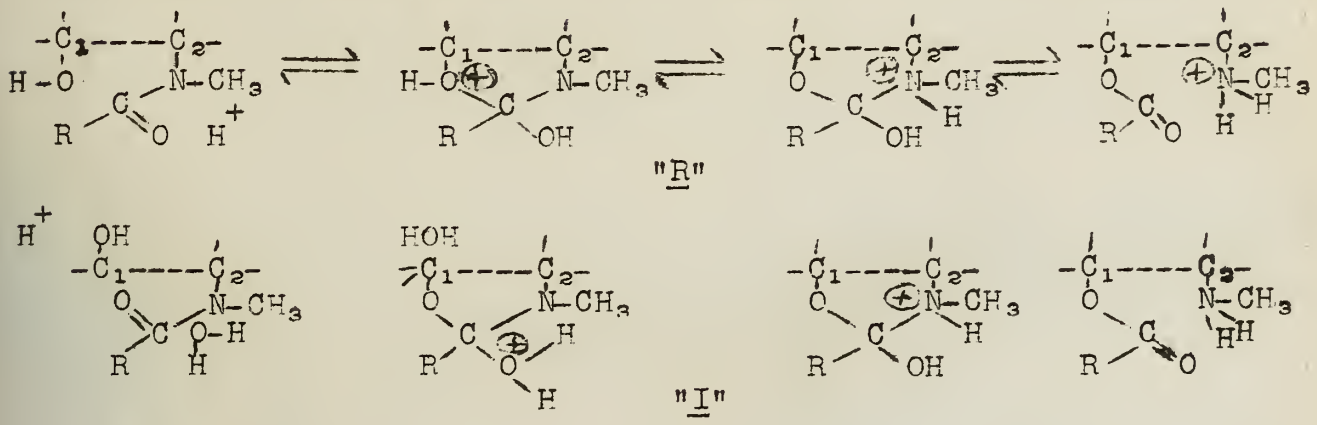
In 1947, in the course of a research to determine the relative configurations of acetyl-ephedrine (V) and acetyl-ψ-ephedrine (VI),[8] it was shown that under acid catalysis (V) and (VI) underwent an N to O acyl migration, the former largely inverting its configuration at C_1 to give O-acetyl-ψ-ephedrine (VII), while the latter retained its configuration to give the same product.



During the same investigation it was shown that in both cases the base-catalyzed O to N migration went with retention of configuration at a rate dependent upon the pH, being practically instantaneous

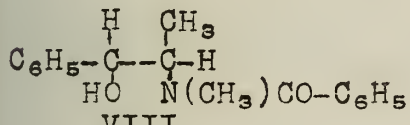
at a sufficiently high pH.

In 1949 mechanisms were proposed for the reactions with retention of configuration (R) and with inversion (I), as follows:[9]

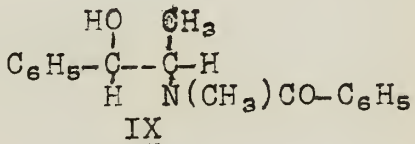


These mechanisms were supported by work done on aroyl migration in which the aryl group was substituted in the ortho position.[9] It was found that the ortho substituent markedly increased the amount o inversion, independent of the electron-displacement characteristics o the group, but roughly proportional to its size. This can be laid t the group's hindering the approach of the hydroxyl-O to the carbonyl-C in the R mechanism much more than the approach of carbonyl-O to C_1 in the I mechanism. Also, the kinetics of migration of N-benzoyl-ψ-ephedrine (VIII) were of the second order.

About the same time it was shown that diastereoisomeric amino-alcohols such as N-benzoyl-ψ-ephedrine (VIII) and N-benzoyl-ephedrin (IX) could be separated by use of the N to O acyl migration; the former giving a water-soluble amine hydrochloride, the latter remaining unchanged.[10]

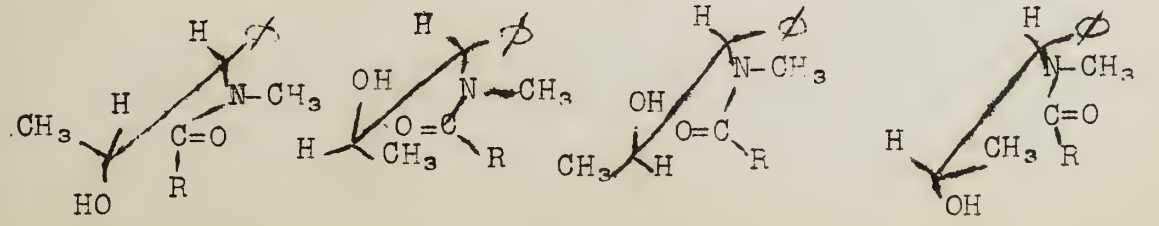


VIII



IX

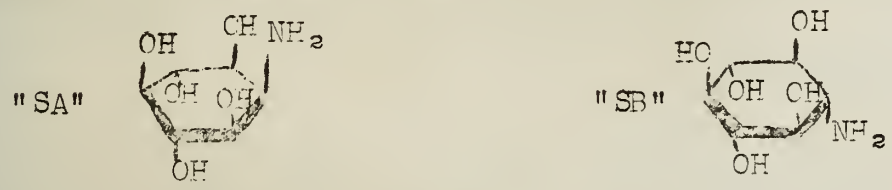
The reasons for the difference, mentioned earlier, in rate and course of reaction of the two isomers can be perceived by a look at the transition states required for them to react according to the I and R mechanisms. It will be seen that in the case of the ψ-isomer reacting by R (via A) the methyl and phenyl groups will be trans, an energetically favorable situation, while to go by the I mechanism (via B) the two groups must be forced into a sterically unfavored cis conformation. Conversely, in the case of the other isomer, the tran conformation is present when it reacts by the I mechanism (via C), and the unfavored cis conformation when it reacts by R (via D).[9]



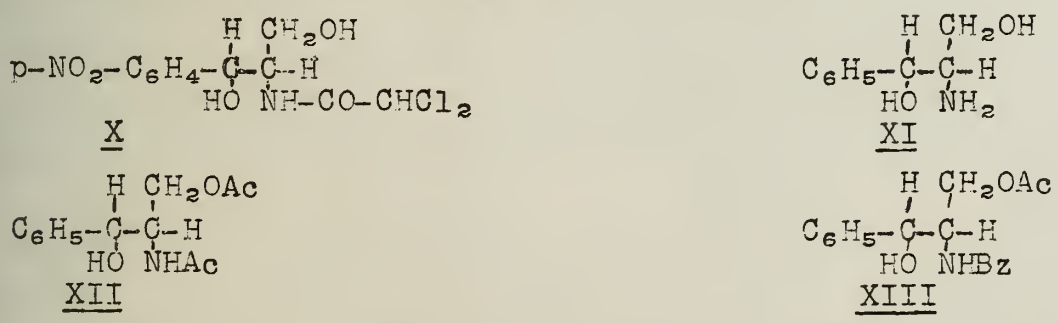
A B C D

It was desirable to verify that the configuration with the amino and hydroxyl groups cis was indeed the one which reacted fastest and with retention, so work of this nature was performed on benzoylated 2-aminocyclohexanols of known configuration.[11,12] The results confirmed the theory, but not conclusively, due to the flexibility of the ring. This objection was overcome by going to the 2-aminocyclopentanol ring, whose cis and trans isomers can also be obtained pure.[13-15] The results confirmed the earlier work completely, i.e. the cis acyl migrated readily and the trans did not.

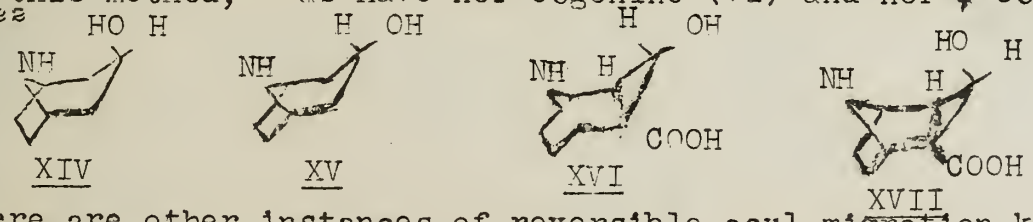
Added confirmation came from the work done on the "SA" and "SB" isomers of ionosamine, in which the rate of N to O acyl migration was measured by determining the rate at which the amino group was liberated.[16,17] The "SA" isomer liberated its amino group three to four times as fast as the "SB" isomer.



Acyl migration has been used to check the steric course of reactions,[18,19] and in a confirmation of the configuration of chloramphenicol (X).[20] Optical rotation data had suggested the configuration to be related to ψ-ephedrine (VIII) rather than to ephedrine (IX). Accordingly, (XI), which had been sterically related to (X), was converted to (XII) and (XIII), and these two compounds subjected to the action of absolute-alcoholic HCl. Both underwent instant migration with retention to give the O_1-O_3 diacyls, while their diastereoisomers gave no rearrangement at all. Therefore (XII) and (XIII) were behaving in the same manner as ψ-ephedrine, and could be regarded as having the ψ configuration.

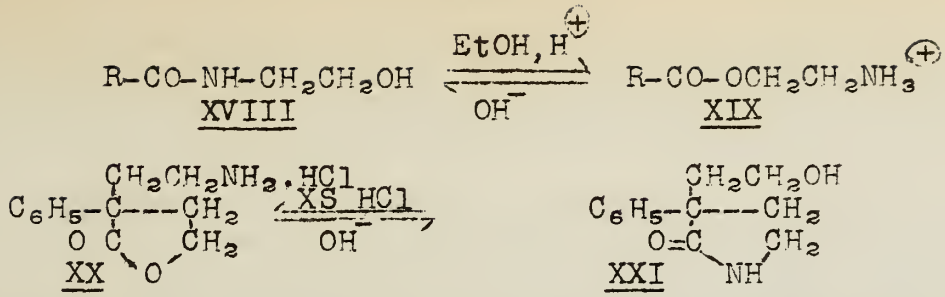


Nor-ψ-tropine (XIV) and nor-tropine (XV) have been differentiated by this method,[21] as have nor-ecgonine (VI) and nor-ψ-ecgonine (XVII).[22]

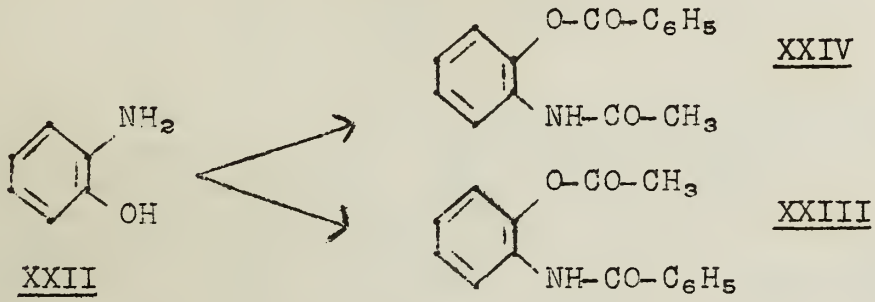


XIV XV XVI XVII

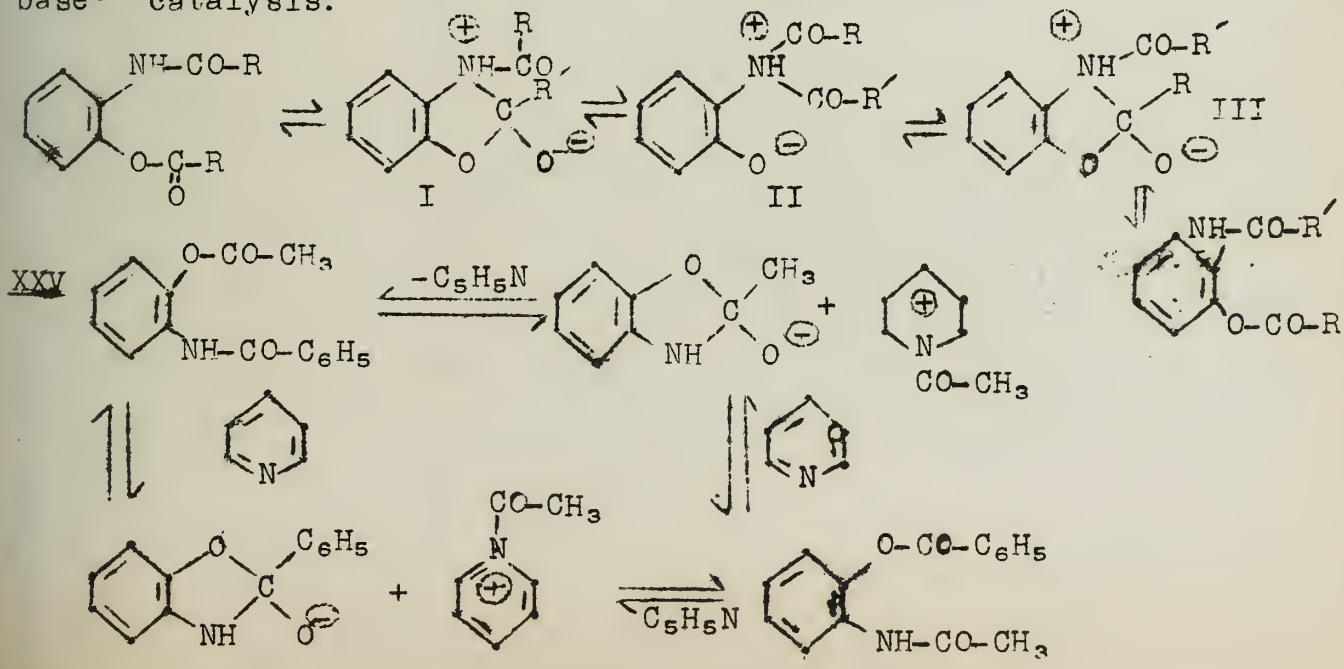
There are other instances of reversible acyl migration known, such as the ethanolamide (XVIII) -- aminoethylester (XIX) interconversion,[32] and the lactone (XX) -- lactam (XXI) interconversion,[33] and there seems to be no doubt that others will be noted in the future.



ACYL EXCHANGE: Acyl migration in the O-N-diacyl-o-aminophenol series is probably actually acyl exchange. Much early work in the field seemed to give evidence that when, for example, acetyl and benzoyl groups were introduced into the o-aminophenol (XXII) molecule in different orders, only one isomer was formed (XXIII) in both cases, instead of different orders of acylation giving different isomers (XXIII) and (XXIV) as would be expected.[23-28]



Although the correct explanation of this phenomenon (i.e. a reversible equilibrium between the isomers, so that recrystallization would recover only the predominant one) was suggested early,[25] it was discarded for lack of evidence. It was, however, brought out again in 1931, at which time it was shown that different isomers actually were produced, although they could not be obtained pure by recrystallization.[29] It was not until 1948 that the isomers were separated and identified, and the equilibrium definitely established as being catalyzed by acids such as water and alcohol, bases such as pyridine, and heat.[30] The following mechanisms have been proposed for acid[34] and base[31] catalysis:



By analogous steps in the presence of an excess of the acetylpyridinium ion the formation of the di- and tri-acetyl derivatives from (XXV) can be explained; the formation of these compounds having been a stumbling-block for the previously suggested mechanisms.

Regarding the acid-catalyzed mechanism, it was found that the migration did not occur in mixed diacyl derivatives of o-alkylaminophenols, so it was postulated that the attainment of phase II probably required simultaneous elimination of a proton. It may, however merely be sterically impossible to get an o-hydroxyphenyl-, two carbonyls and an alkyl on one nitrogen. This is supported by the fac that when one of the acyls is a sulfonyl no migration is observed, even if a hydrogen is present on the nitrogen.

BIBLIOGRAPHY

1. W. Böttcher, Ber., 16, 629-34 (1883).
2. K. Auwers, Ann., 365, 278-90 (1909). et seq.
3. K. Auwers, Ber., 33, 1923-9 (1900).
4. V. Bruckner, Ann., 518, 226-44 (1935).
5. V. Bruckner and A. Kramli, J. prakt. Chem., 143, 287-97 (1935).
6. A. Kramli and V. Bruckner, ibid., 148, 117-25 (1937).
7. E. Vinkler and V. Bruckner, ibid., 151, 17-24 (1938).
8. L.H. Welsh, J. Am. Chem. Soc., 69, 128-36 (1947).
9. L.H. Welsh, ibid., 71, 3500-6 (1949).
10. G. Fodor and J. Kiss, Nature, 163, 287 (1949); J. Org. Chem., 14, 337-45 (1949).
11. G. Fodor and J. Kiss, Nature, 164, 917 (1949).
12. G. Fodor and J. Kiss, J. Am. Chem. Soc., 72, 3495-7 (1950).
13. G.E. McCasland and D.A. Smith, ibid., 72, 2190-5 (1950).
14. G. Fodor and J. Kiss, Research, 4, 382-3 (1951).
15. G. Fodor and J. Kiss, J. Chem. Soc., 1952, 1589-92.
16. L. Anderson and H.A. Lardy, J. Am. Chem. Soc., 72, 3141-7 (1952).
17. G.E. McCasland, ibid., 73, 2295 (1951).
18. G. Fodor and K. Koczka, J. Chem. Soc., 1952, 840-4.
19. G. Fodor et al., J. Org. Chem., 15, 227-32 (1950).
20. G. Fodor et al., Nature, 167, 690 (1951); J. Chem. Soc., 1951, 1858.
21. G. Fodor and K. Nador, Nature, 169, 462-3 (1952).
22. G. Fodor, ibid., 170, 278-9 (1952).
23. A. Einhorn and B. Pfyl, Ann., 311, 34-73 (1900).
24. J.H. Ransom, Am. Chem. J., 23, 1-50 (1900).
25. J.H. Ransom and R.E. Nelson, J. Am. Chem. Soc., 36, 390-3 (1914).
26. L.C. Raiford et al., ibid., 41, 2068-80 (1919); ibid., 44, 1792-8 (1922); ibid., 45, 469-75 (1923); ibid., 46, 430-7, 2246-55, 2305-18 (1924); ibid., 47, 1111-23, 1454-8 (1925); ibid., 48, 483-9 (1926); ibid., 50, 1201-4 (1928); ibid., 56, 1586-90 (1934); J. Org. Chem., 4, 207-19 (1939); ibid., 5, 300-12 (1940); J. Am. Chem. Soc., 65, 2048-51 (1934); J. Org. Chem., 10, 419-28 (1945); J. Am. Chem. Soc., 67, 2163-5 (1945).
27. R.E. Nelson et al., J. Am. Chem. Soc., 48, 1677-9, 1680-3 (1926); ibid., 49, 3129-31 (1927); 50, 919-23 (1928); ibid., 51, 2761-4 (1929); ibid., 53, 996-1001 (1931).
28. F. Bell, J. Chem. Soc., 1930, 1981-7.
29. F. Bell, ibid., 1931, 2962-7.
30. A.L. LeRosen and E.D. Smith, J. Am. Chem. Soc., 70, 2705-9 (1948).
31. A.L. LeRosen and E.D. Smith, ibid., 71, 2815-18 (1949).
32. A.P. Phillips and R. Baltzly, ibid., 69, 200-4 (1947).
33. E. Walton and M.B. Green, J. Chem. Soc., 1945, 315-19.
34. G.W. Anderson and F. Bell, ibid., 1949, 2668-71.

SOME CHROMIC ACID OXIDATIONS

Reported by Y. Gust Hendrickson December 12, 195

Oxidation of Alcohols.- Primary and secondary alcohols, oxidize by chromic acid in aqueous sulfuric acid, give good yields of normal oxidation products. Since isopropyl alcohol yields acetone quantitatively at a rate which can easily be measured, Westheimer[1] chose this system for a study of the mechanism. This excellent detailed study revealed the following facts about the reaction.

$$3CH_3CHOHCH_3 + 2HCrO_4^- + 8H^+ \rightarrow 3CH_3COCH_3 + 2Cr^{+++} + 8H_2O$$

1. At constant low pH, using excess alcohol, the reaction is first order in isopropyl alcohol, acid chromate ion ($HCrO_4^-$), and second order in hydrogen ion concentrations; the rate expression being[2]

$$-d(CrO_3)/dt = k(CH_3CHOHCH_3)(HCrO_4^-)(H^+)^2$$

2. Manganous ion (Mn^{++}) added to the reaction is oxidized to manganese dioxide, the competition yielding a limiting induction factor (the mole ratio of manganese dioxide producted to alcohol oxidized) of 1/2.[2,3]
3. Added manganese dioxide inhibits the rate of oxidation of alcohol by a factor approaching 50% as a limit.[3]
4. The rate of oxidation of 2-deutero-2-propanol is only 1/7 the rate of isopropyl alcohol.[4,5] The rates for 1,1,1,3,3,3-hexadeutero-2-propanol and isopropyl alcohol are about the same.[5]

From these facts the following conclusions can be made:
A. The active oxidizing species is acid chromate ion. Constant rate constants were not obtained with an expression containing CrO_3 in place of $HCrO_4^-$. However, by considering the equilibrium,

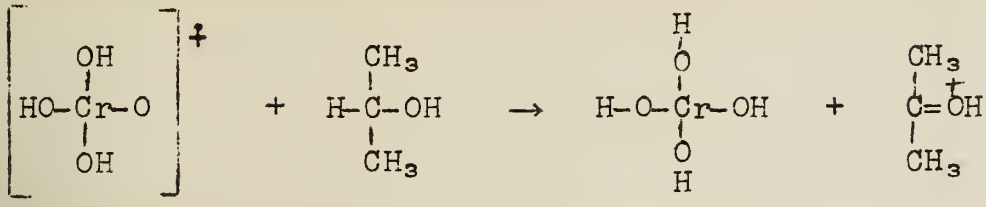
$$H_2O + Cr_2O_7^= \rightleftarrows 2HCrO_4^- \; ; \quad K = 0.023 \text{ Mole/liter}$$

assuming only $HCrO_4^-$ as the active species, constant k's were obtained.[2]
B. An intermediate species of Cr IV participates in the reaction. Since Mn^{++} is not oxidized by chromic acid under these conditions, a more active oxidizing agent must be formed during the reaction. The induction factor requires an entity of Cr IV.[3]
C. The secondary carbon-hydrogen bond must be cleaved in the rate determining step.[4,5]

From over 45 mechanisms considered, four reasonable mechanisms which explain all of the experimental facts emerge if one will assume that 1.- only these species are possible participants; $HCrO_4^-$, H^+, $CH_3CHOHCH_3$, $(CH_3)_2CHO\cdot$, $HO\cdot$, CH_3COCH_3, Cr V, Cr IV, Cr III, Cr II and 2.- reactions between two unstable species are negligible. Since autocatalysis is not observed many schemes can be discarded. Common to the four remaining mechanisms is the first, rate-determining step[1,3]

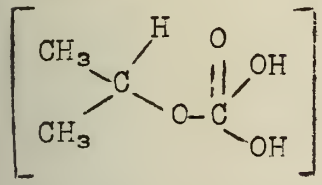
$$2H^+ + HCrO_4^- + CH_3CHOHCH_3 \rightarrow \text{Cr IV} + CH_3\overset{O}{\overset{\|}{C}}-CH_3 + 2H^+$$

which can be pictured as a concerted one-step reaction



or a two-step process involving a chromate ester.

$$HCrO_4^- + 2H^+ + CH_3CHOHCH_3 \overset{\text{fast}}{\rightleftarrows} [(CH_3)_2CHOCrO_3H]^+ + H_2O$$



$$+ H_2O \xrightarrow{\text{slow}} CH_3-\overset{O}{\overset{\|}{C}}-CH_3 + H_2CrO_3 + H_3O^+$$

In the absence of Mn^{++} the following steps describe how Cr IV is converted to Cr III with the oxidation of two more molecules of alcohol and the reduction of one more Cr VI. One of the schemes is as follows:

$$\text{Cr IV} + CH_3CHOHCH_3 \rightarrow \text{Cr II} + CH_3\overset{O}{\overset{\|}{C}}-CH_3$$

$$\text{Cr VI} + \text{Cr II} \rightarrow \text{Cr III} + \text{Cr V}$$

$$\text{Cr V} + CH_3CHOHCH_3 \rightarrow \text{Cr III} + CH_3\overset{O}{\overset{\|}{C}}-CH_3$$

In the presence of Mn^{++}, only the following scheme will explain both the inhibition and the induction factor.

$$Mn^{++} + \text{Cr IV} \rightarrow \text{Mn III} + \text{Cr III}$$

$$2\text{Mn III} + 2H_2O \rightarrow MnO_2 + Mn^{++} + 4H^+$$

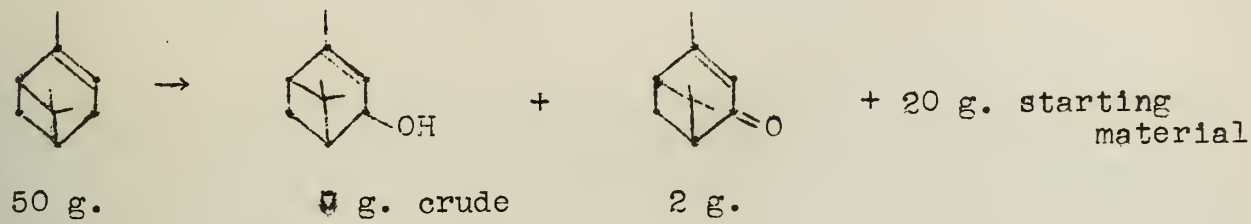
The esterification mechanism is further substantiated by recent observations. Dilute benzene and toluene solutions of di-t-butyl and diisopropyl chromates have been prepared.[6,7] Since the compounds are very unstable they have not yet been isolated; however, analysis of the solutions indicate a compound containing two molecules of alcohol per atom of chromium. These compounds can be extracted into benzene but cannot be removed from benzene solution by extraction with aqueous bicarbonate or carbonate, indicating that they are neutral esters. Both hydrolysis and internal oxidation-reduction of diisopropyl chromate in benzene are catalysed by bases like pyridine, quinoline and dimethylamine.[6,7]

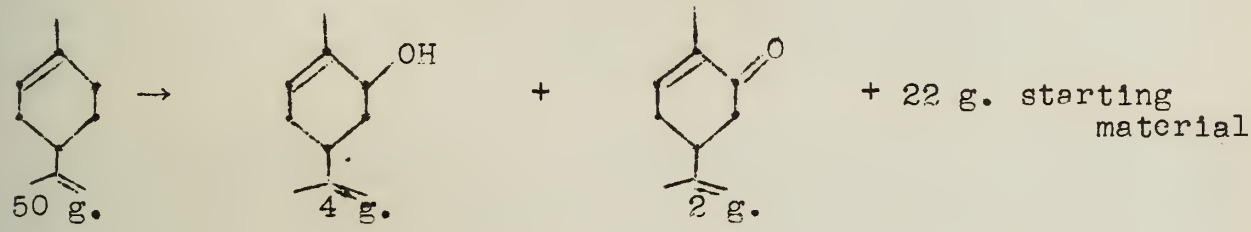
hydrolysis $ROCrO_2OR + H_2O \rightleftarrows CrO_3 + 2ROH$
$CrO_3 + H_2O + C_5H_5N \rightleftarrows C_5H_5NHHCrO_4$

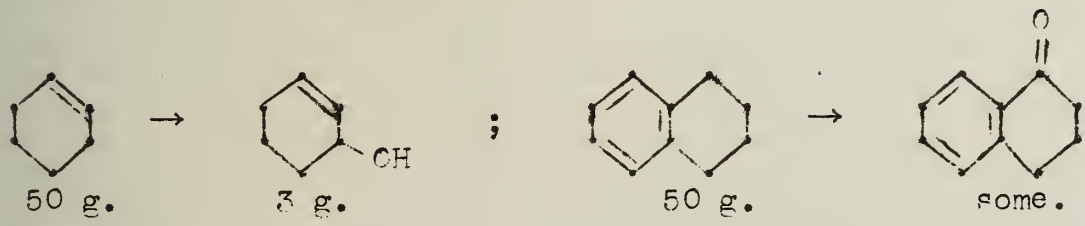
oxidation-reduction $(CH_3)_2CHOCrO_2OCH(CH_3)_2 \rightarrow (CH_3)_2CO + (CH_3)_2CHOH + CrO$

The oxidation of isopropyl alcohol is also strongly catalysed by pyridine though the concentration of the free base is very small in this acidic medium.[6]

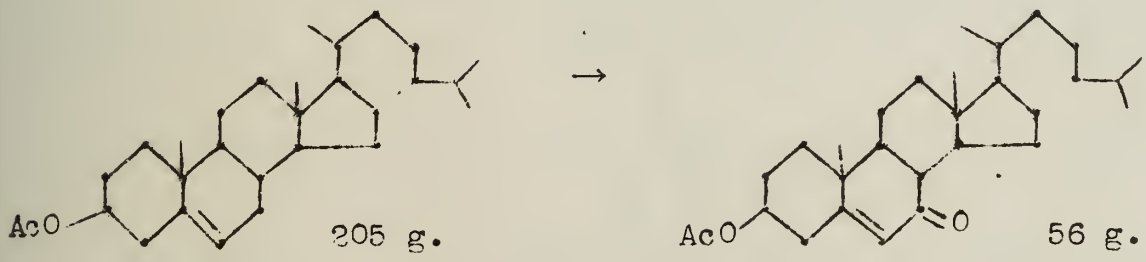
Oxidation of Olefins.- On vigorous oxidation with chromic aci in aqueous sulfuric acid, olefins generally give acids and ketones rising from the cleavage of the double bond. With some systems however, under less vigorous conditions products of oxidation at the allyl position have been found. By slowly dropping the hydocarbon dissolved in carbon tetrachloride into a solution of chromi acid in acetic anhydride at 0°, Treibs and Schmidt obtained small amounts of allylic oxidation.[8]



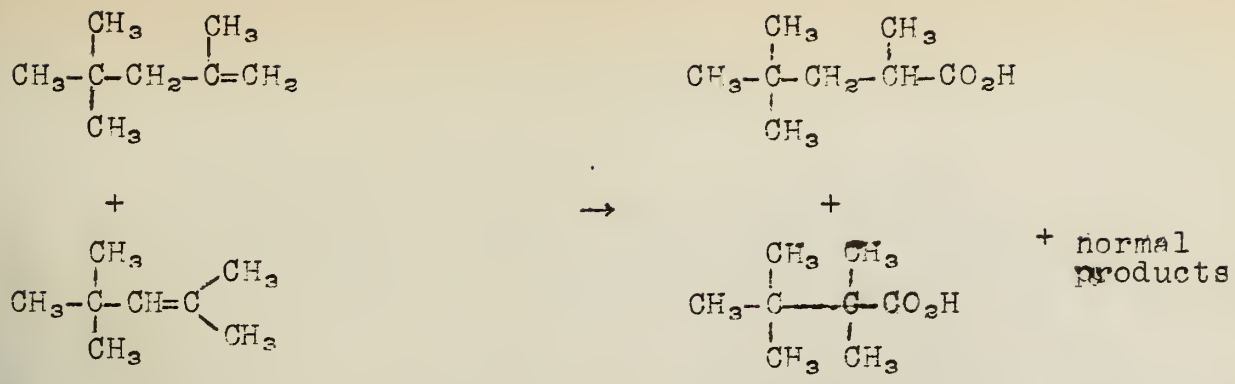




7-Keto-cholesteryl acetate in somewhat better yield was obtained b a similar oxidation of cholesteryl acetate in glacial acetic acid.[9,10]

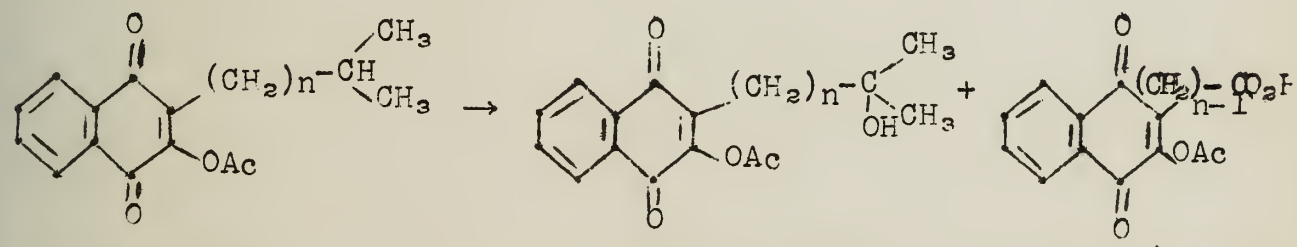


In addition to acetone, 2,2-dimethyl-4-pentanone and trimethyl-acetic acid, Byers and Hickinbottom[11] obtained some 2,4,4-trimethylpentanoie acid and 2,2,3,3-tetramethylbutanoic acid from the chromic acid oxidation of a mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene.



By controlled oxidation in acetic anhydride the authors were able to isolate the epoxides of the two olefins. On hydrolysis with aqueous sulfuric acid, they gave 2,4,4-trimethyl-1,2-pentanediol, 2,4,4-trimethylpentanal, 2,4,4-trimethyl-2,3-pentanediol, and 2,2,3,3-tetramethylbutanal, which would be oxidized to the products obtained from the olefins by chromic acid. These epoxides may be intermediates in the aqueous oxidation of the olefins.

Paraffin Side Chains.- A striking difference in the behavior of chromic acid compared with other oxidizing agents was discovered by Fieser.[12,13] While permanganate, hydrogen peroxide, and hypochlorite oxidize the nucleus of hydroxyalkylnaphthoquinones, chromic acid, like enzymes in the human body, attack the side chain. The point of attack and the products vary with the side chain, but some generalizations can be made: 1.- No attack occurs at the α or β carbon atoms near the quinone ring. 2.- Tertiary carbon atoms are most easily oxidized while methyl groups remain unchanged. 3.- Attack usually occurs at or near the γ carbon atom. 4.- After the introduction of a carbonyl group β oxidation can occur, producing degradation of the side chain. These side chains yield:



n = 2,4,6,7 — n = 2,18%; 4, 38%; 6, 36% yield — n = 4,34%; 6, 21%; 7, 7

$-C_{10}H_{21}-n \rightarrow -(CH_2)_6\overset{O}{\overset{\|}{C}}-(CH_2)_2-CH_3$ (22%) + other ketones + $-(CH_2)_n-CO_2H$ n = 2,3,4,5,6,7 total 24%

$-CH_2-\overset{CH_3}{\overset{|}{CH}}-(CH_2)_5-CH_3 \rightarrow -CH_2-\overset{CH_3}{\overset{|}{CH}}-(CH_2)_4-\overset{O}{\overset{\|}{C}}-CH_3$ (7%) + $-CH_2-\overset{CH_3}{\overset{|}{CH}}-(CH_2)_n-CO_2H$ n = 4,3,1 total 22%

$-(CH_2)_5-C_6H_5 \rightarrow -(CH_2)_4-\overset{O}{\overset{\|}{C}}-C_6H_5$ (90%)

BIBLIOGRAPHY

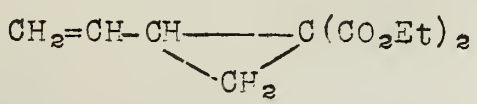
1. F. H. Westheimer, Chem. Revs., 45, 419 (1949).
2. F. H. Westheimer, J. Chem. Phys., 11, 506 (1943).
3. W. Watanabe and F. H. Westheimer, ibid., 17, 61 (1949).
4. F. H. Westheimer and N. Nicolaides, J. Am. Chem. Soc., 71, 25 (1949).
5. M. Cohen and F. H. Westheimer, ibid., 74, 4386 (1952).
6. F. Holloway, M. Cohen and F. H. Westheimer, ibid., 73, 65 (1951).
7. A. Leo and F. H. Westheimer, ibid., 74, 4383 (1952).
8. W. Treibs and H. Schmidt, Ber., 61, 459 (1928).
9. A. Windaus, H. Lettre' and F. Schenk, Ann., 520, 98 (1935).
10. W. Buser, Helv. Chim. Acta, 30, 1379 (1947).
11. A. Byers and W. J. Hickinbottom, J. Chem. Soc., 1948, 1334.
12. L. F. Fieser, J. Am. Chem. Soc., 70, 3237 (1948).
13. L. F. Fieser, ibid., 74, 3910 (1952).

A NEW SYNTHETIC ROUTE TO CYCLOPROPANES

Reported by S. L. Jacobs December 12, 1952

The following discussion is based primarily on the work recently done by Linstead and co-workers of the Imperial College of Science and Technology of London.[1]

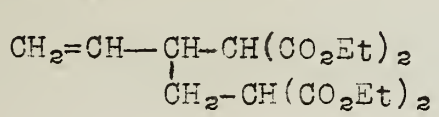
The reaction of ethyl sodiomalonate with 1,4-dibromobutene-2 in ethyl alcohol was employed in an attempt to prepare 3-hexene-1,6-dicarboxylic acid. The success of this reaction was anticipated on the grounds that primary allyl halides had been shown to condense with sodiomalonate by a normal S_N2 mechanism.[2] The main product of the reaction, however, was found to be (I).



(I)

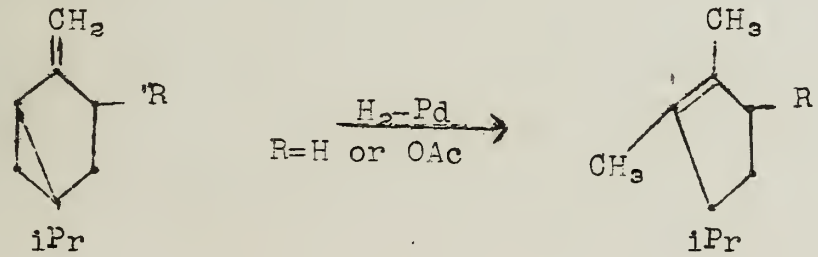
A minor fraction was obtained consisting mainly of (II) and (III)

(II)



(III)

The structure of (I) was proved by U.V. absorption and ozonolysis. Catalytic hydrogenation of (I) gave ethyl n-butylmalonate, $CH_3-CH_2-CH_2-CH_2-CH(CO_2Et)_2$, with the up-take of two moles of hydrogen. Such ring fission usually requires more drastic conditions than were used here (Adams' catalyst). This ring fission may be thought of as 1,4-addition to a system comprised of a double bond conjugated with a three-membered ring. The following are other examples where cleavage of a cyclopropyl ring occurs on hydrogenation:-



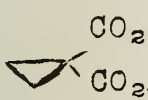
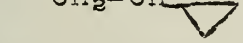
[3, 4]

Cyclopropylalkenes such as 2-cyclopropylpentene-2, 2-cyclopropylpropene, and vinylcyclopropane have been hydrogenated under suitable conditions to give mixtures of cyclopropyl alkanes and straight- or branched-chain paraffins.[5,6,7] In some cases, similar conditions of hydrogenation do not cleave the cyclopropane ring as is the case with many 2-cyclopropyl-1-alkenes,[5,8,9] the trans-chrysanthemum mono- and dicarboxylic acids[10] and certain terpenes.[3,11]

The ability of a cyclopropane ring to conjugate with various chromophores is shown by physical evidence[7,12] and by the reductive fission of vinylcyclopropanes mentioned above. The electronic interaction with other chromophores which is involved here is due to the fact that the electrons in cyclopropane rings are more weakly bound than the usual σ-electrons and exhibit characteristics usually associated with unlocalized π-electrons.

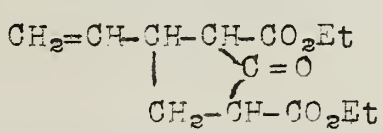
Molecular refractivity data indicate that the exaltation observed for the new compound (I) is due mainly to interaction of the cyclopropane ring with the adjacent vinyl group.

Molecular Refractivities

		R_D(obs.)	R_D(calc.)	Exaltation
	(IV)	45.60	45.54	0.06
	(V)	23.85	23.37	0.48
(I)		54.96	54.36	0.60
			54.41*	0.55
			54.84**	0.12

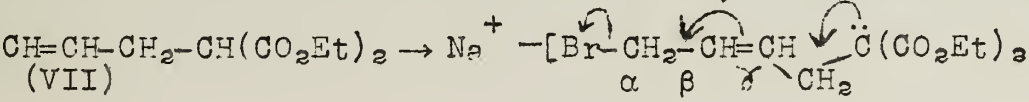
* Calculated from R_D(obs.) for (IV)
** Calculated from R_D(obs.) for (V)

The structure of (II) was proved by conversion to suberic acid, and that of (III) by cyclization with NaOEt to ethyl 2-keto-4-vinylcyclopentane-1,3-dicarboxylate (VI).

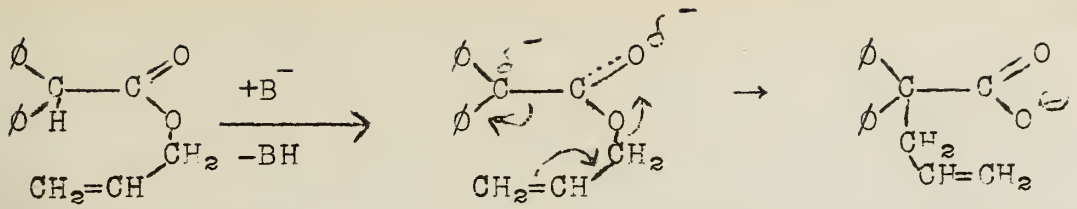


(VI)

Absence of solvolysis products in the malonate-dibromobutene reaction indicates the absence of a carbonium ion mechanism, and a migration of bromine from an α- to a γ-carbon before replacement is considered unlikely.[13] Also, 3,4-dibromobutene-1 (to which the 1,4-compound may isomerize[14]) does not give the same reaction with ethyl sodiomalonate. The reaction is therefore said to proceed without initial rearrangement by a bimolecular nucleophilic attack and, after substitution of the first bromine, may be represented as



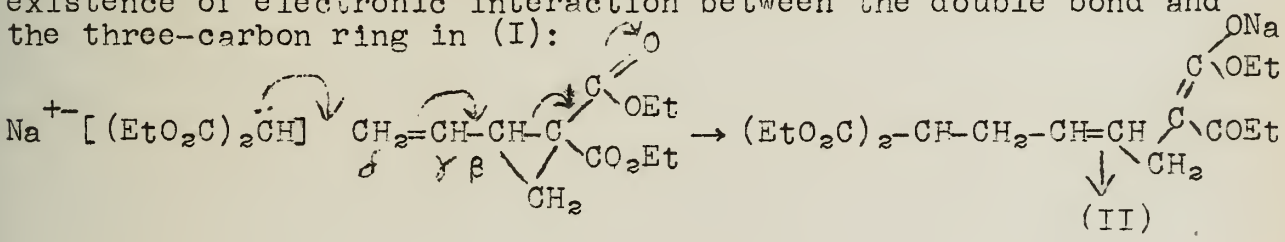
The high proportion of intramolecular γ-attack (rather than α-attack) is probably due to the <u>trans</u> configuration of the double bond. Intramolecular rearrangements of allyl derivatives at C(γ) have previously been suggested to account for the rearrangements of allyl derivatives[15,16], as



Since there is no obvious reason why bimolecular α-attack would not predominate to give (II), the formation of (III) in greater proportion than (II) cannot be attributed to an intermolecular γ-attack of (VII). It is more probable that (II) and (III) are formed by further attack of (I). Similar reactions are known.[17] However, the main product (60%) of the reaction of ethyl sodiomalonate with (I) is (VI), formed with the elimination of the elements of ethyl carbonate. Such reactions for the conversion of a three- to a five-membered ring are known, as that of ethyl 1-cyanocyclopropane-1-carboxylate with ethyl cyanoacetate in the presence of some of the sodio derivative of the latter to give the imino compound.[18]

The reaction of ethyl sodiomalonate with (I) gives, in addition to (VI), a smaller fraction consisting of a mixture of (II) and (III). (III) can be cyclized to (VI) with NaOEt.

Therefore, it was shown that the addition of ethyl sodiomalonate to (I) occurs mainly by attack at $C_{(\beta)}$ (see formula below) to give (III) which then may undergo cyclization to (VI). Some $C_{(\delta)}$ attack occurs to provide chemical confirmation for the existence of electronic interaction between the double bond and the three-carbon ring in (I):



The experimental conditions for the reaction of ethyl sodiomalonate with 1,4-dibromobutene-2 do not favor cyclization of (III) since no appreciable alkoxide concentration is built up. Alkoxide is, however, produced in the condensation of malonate with (I). Here, therefore, extensive cyclization occurs.

The foregoing discussion provides further evidence for the conjugation of the three-membered ring with the double bond through elucidation of the malonate condensation with 1,4-dibromobutene-2, and a convenient new route to cyclopropane derivatives has been realized.

BIBLIOGRAPHY

1. R. W. Kierstead, R. P. Linstead and B. C. L. Weedon, J. Chem. Soc. 1952, 3610, 3616.

2. R. E. Kepner, S. Winstein and W. G. Young, J. Am. Chem. Soc. 71, 115 (1949).
3. A. G. Short and J. Read, J. Chem. Soc. 1939, 1040.
4. F. Richter, W. Wolff and W. Presting, Ber. 64, 871 (1931).
5. V. A. Slabey and P. H. Wise, J. Am. Chem. Soc. 74, 3887 (1952).
6. R. Van Volkenburgh, K. W. Greenlee, J. M. Derfer and C. E. Boord, J. Am. Chem. Soc. 71, 172 (1949).
7. ibid. 71, 3595 (1949).
8. V. A. Slabey and P. H. Wise, Nat'l. Advisory Comm. Aeronautics, Tech. Note 2258-9 (1951); C. A. 45, 7531 (1951).
9. V. A. Slabey and P. H. Wise, J. Am. Chem. Soc. 71, 1518 (1949).
10. H. Staudinger and L. Ruzicka, Helv. Chim. Acta. 7, 201 (1924).
11. L. Tschugaev and W. Fomin, Compt. Rend. 151, 1058 (1910).
12. L. T. Smith and E. R. Rogier, J. Am. Chem. Soc. 73, 3840 (1951)
13. A. G. Catchpole and E. D. Hughes, J. Chem. Soc. 1948, 4.
14. E. H. Farmer, C. D. Lawrence and J. F. Thorpe, J. Chem. Soc. 1928, 729.
15. S. Winstein, Bull. Soc. Chim. 18, C43 (1951).
16. A. G. Catchpole, E. D. Hughes and C. K. Ingold, J. Chem. Soc. 1948, 8.
17. W. A. Bone and W. H. Perkin, J. Chem. Soc. 67, 108 (1895).
18. S. R. Best and J. F. Thorpe, J. Chem. Soc. 1909, 685.

SULFONATION OF ACID-SENSITIVE COMPOUNDS

Reported by Clayton T. Elston December 19, 1952

With compounds that decompose or polymerize in the presence of strong mineral acids the common sulfonating agents are of very limited usefulness. Complexes of SO_3 with various organic bases have proved to be quite effective in the sulfonation of many such acid-sensitive materials. In 1926 Baumgarten[1] prepared a complex of pyridine and sulfur trioxide and observed that this complex decomposed to regenerate its components. Thus, a reagent was now at hand which under controlled conditions could release its SO_3 to nucleophilic compounds and effect sulfonation. Baumgarten then proceeded to test the effect of the reagent on a series of organic compounds. He found, for instance, that phenol could be sulfated by this reagent without any nuclear sulfonation as occurs with concentrated sulfuric acid. Other workers, realizing the advantages of the method used it in the sulfonation of proteins, amines, amides, polysaccharides and polyvinyl alcohol.

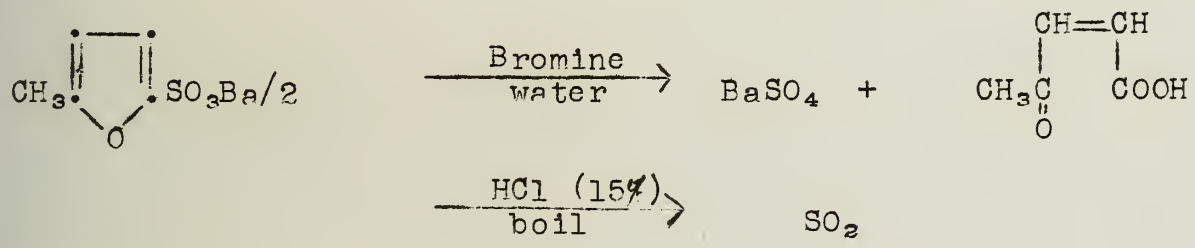
Other SO_3 complexes are known, as for example those with dimethylaniline[2], trimethylamine[3] and dioxane[4]. Dimethylaniline sulfotrioxide is an extremely unstable substance which readily transforms into p-dimethylanilinesulfonic acid. Trimethylamine sulfotrioxide on the other hand is very stable. However, it is this stability which limits its usefulness since it gives up its SO_3 only under rather drastic conditions. Dioxane sulfotrioxide, first prepared by Suter[4] in 1938, is a rather unstable material and in contrast with pyridine sulfotrioxide decomposes rapidly in water, forming sulfuric acid. Suter has made extensive investigations on the use of dioxane sulfotrioxide in the sulfonation of unsaturated compounds.[5]

Beginning in 1946 Terentyev and his co-workers have conducted an extended series of researches on the use of pyridine sulfotrioxide as a sulfonating agent for acid-sensitive compounds. The method involved heating the reactants together in a sealed tube at a temperature of 100-110°C. for a period of eight to ten hours. Usually a threefold excess of pyridine sulfotrioxide gave the best results. Modifications of this general procedure involved reaction at slightly lower or higher temperatures and the use of an inert solvent such as ethylene chloride. In all cases the sulfonated compounds were isolated as their barium salts. This seminar will deal briefly with the sulfonation of: (i) furans and coumarone (ii) pyrroles (iii) indoles (iv) unsaturated compounds.

Furans

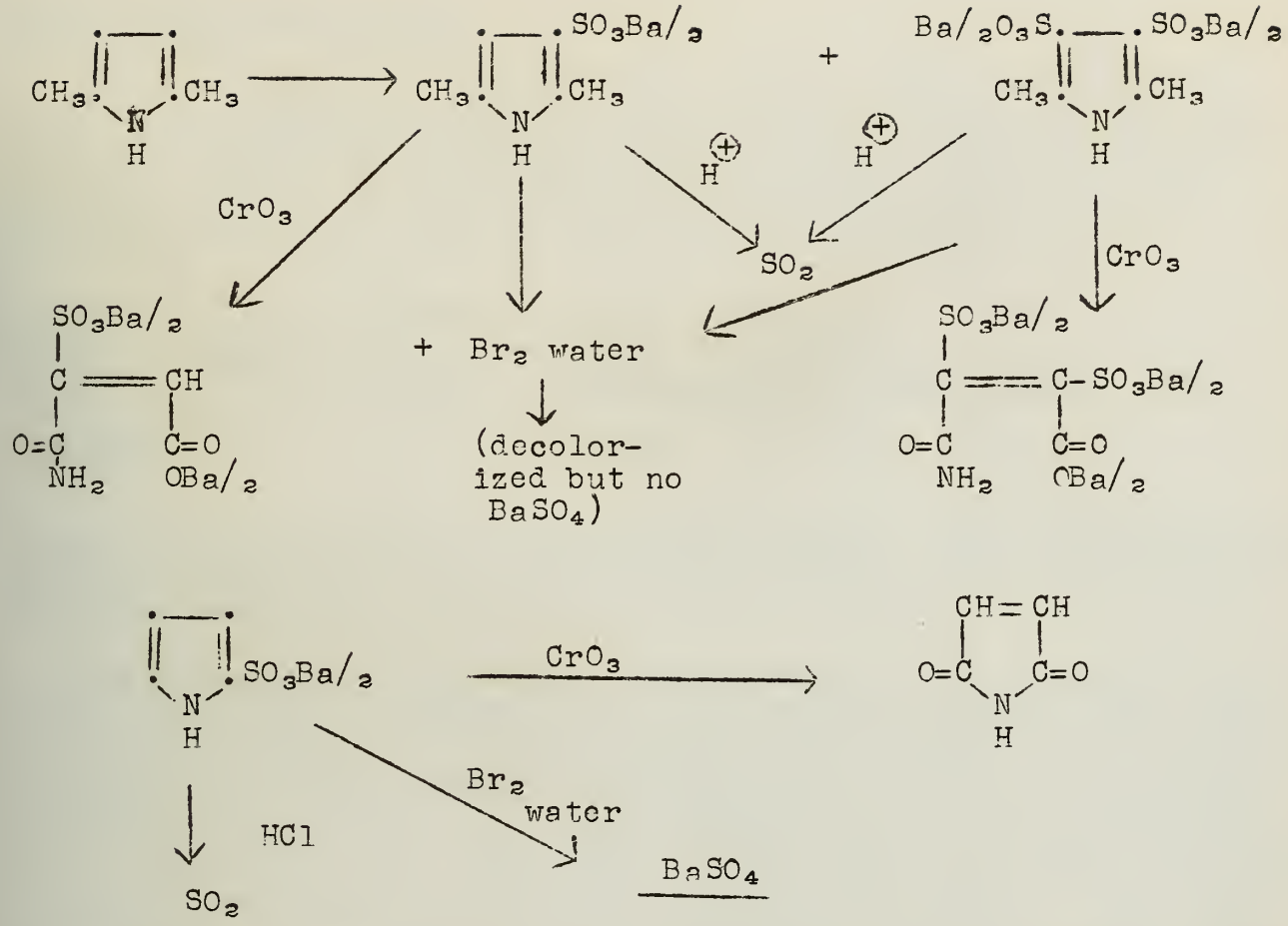
Mineral acids readily promote ring opening and polymerization reactions with furan and its homologs and prior to Terentyev's work very little was known about furansulfonic acid derivatives. Using the general method outlined above he successfully sulfonated furan, 2-methylfuran, 2,5-dimethylfuran, 2-acetylfuran and coumarone, obtaining furan-2-sulfonic acid, 2-methylfuran-3,5-disulfonic acid, 2,5-dimethylfuran-3-sulfonic acid, 2-acetylfuran-5-sulfonic acid and coumarone-2-sulfonic acid respectively[6,8,10,11,12]

At lower temperatures 2-methylfuran yielded 2-methylfuran-5-sulfonic acid. High yields (55-90%) of the crystalline salts were obtained in these reactions. Furfural did not react under these conditions and the methyl ether of furfuryl alcohol yielded only a resinous product. 2-Furoic acid reacted at 140° with displacement of the carboxyl group to give furan-2-sulfonic acid. The salts were stable in the presence of hot alkali but were hydrolyzed rapidly with dilute HCl. This hydrolysis, yielding SO_2, proceeded with both the α- and β-sulfo compounds but was much more rapid in the case of the former. However, coumarone-2-sulfonic acid yielded sulfuric acid and coumarone. Compounds in which the sulfonic acid group was α to the heterocyclic atom were readily oxidized by bromine water giving a precipitate of barium sulfate. The method of structure proof may be illustrated with 2-methylfuran-5-sulfonic acid.



Pyrroles

Several examples of the sulfonation of pyrrole derivatives are known. In 1885 Ciamician and Silber[25] sulfonated 2-acetylpyrrole by treating it with sulfuric acid vapor. By this method they separated and analyzed the potassium salt of the monosulfonic acid. However, they did not determine the position of the sulfo group in the molecule. In 1935 Pratesi[26] obtained an excellent yield of 2,4-dimethyl-5-carbethoxypyrrole-3-sulfonic acid by treating the pyrrole with a chloroform solution of chlorosulfonic acid. With this reagent 2,4-dimethyl-3-carbethoxypyrrole resinified, as was the case with pyrrole itself and its other homologs which were not stabilized by electron-withdrawing substituents. With pyridine sulfotrioxide, sulfonation of the latter type of compounds was possible[13,15,18,20,22]. Terentyev obtained pyrrole-2-sulfonic acid, 1-methylpyrrole-2-sulfonic acid, 2-methylpyrrole-5-sulfonic acid and 2,4-dimethylpyrrole-5-sulfonic acid by the sulfonation of the corresponding pyrrole derivatives. Yields were generally high. β-sulfonic acids were obtained from 1,5-disubstituted pyrroles by varying the experimental conditions. Ether or benzene was used as solvent and the reaction mixture was heated to 100° for six hours. For example, a mixture of mono- and disulfonic acids was obtained from 2,5-dimethylpyrrole. Some of the reactions of these materials are given below.



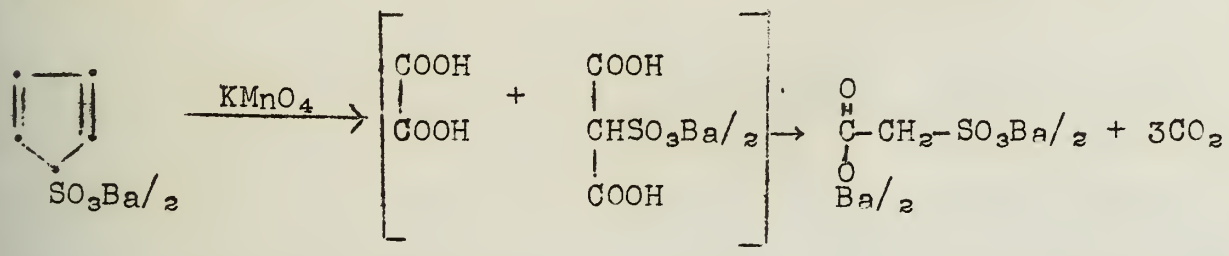
2-Acetylpyrrole can be sulfonated with fuming sulfuric acid to yield 75% of a monosulfonic acid. Contrary to expectations, oxidation of this material with a dichromate sulfuric acid mixture yielded a sulfomaleamic acid, indicating that sulfonation had occurred in the β-position. Sulfonation of 2-acetylpyrrole with pyridine sulfotrioxide gave a mixture of 2-acetylpyrrole-4-sulfonic acid and 2-acetylpyrrole-3,5-disulfonic acid. Even the highly unstable 2-chloropyrrole can be sulfonated with pyridine sulfotrioxide to yield the corresponding 5-sulfonic acid.

Indoles

In its behavior toward pyridine-SO_3 indole resembles pyrroles, but it is somewhat less acid-sensitive[7,9,13,24]. A sulfonation temperature of 120° was found necessary since at lower temperatures the reaction apparently stops at the N-sulfo derivative. It is noteworthy that sulfonation occurs at the 2-position, whereas substitution reactions with indole generally occur at the 3-position. Indole itself gave an almost quantitative yield of indole-2-sulfonic acid and 3-methylindole gave 3-methylindole-2-sulfonic acid in a yield of 55%. 2-Methylindole failed to react under the conditions employed. However, sulfonation in the 3-position was effected with 2-phenylindole. The structure of indole-2-sulfonic acid was confirmed by fusion of the salt with potassium hydroxide. Oxindole was the product of fusion. Oxidation of 2-phenylindole-3-sulfonic acid with potassium permanganate yielded benzoylanthranilic acid.

Unsaturated Hydrocarbons

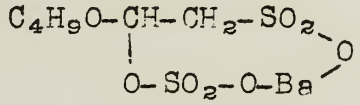
Cyclopentadiene polymerizes very easily. This sensitivity to acids is so marked that even a minute trace of acid produces rapid tarring. Sulfonation with pyridine-SO_3 yielded 42% of the monosulfonic acid[21]. The fact that sulfonation had occurred at the methylene group was shown by oxidation to sulfoacetic acid.



Indene likewise yielded a monosulfonic acid[16]. The authors assumed that the sulfo group had entered the 2-position but offered no definite proof.

Pyridine-SO_3 did not react with paraffins, cycloparaffins, benzene homologs or olefins with a non-terminal double bond. Good yields of sulfonic acids were obtained from cyclohexene, methylenecyclohexane, camphene, styrene and conjugated dienes such as 1,3-butadiene and isoprene[16,23]. The formation of sulfonic acid derivatives was assumed to take place through addition of two moles of SO_3 at the double bond. In order to obtain the sulfonic acid salts the sulfonated mass was treated with barium carbonate. Then, depending upon the stability of the intermediate product, either the barium salt of the isethionic acid derivative was obtained, or the splitting off of a molecule of sulfuric acid took place and the barium salt of the unsaturated sulfonic acid was formed. The latter was observed in the case of camphene, styrene, butadiene and isoprene.

Vinyl ethers react in a similar manner. For example, n-butyl vinyl ether yielded a barium salt having the emperical formula $C_6H_{12}O_8Ba$. The salt did not bleach bromine water and upon hydrolysis yielded butyl alcohol, barium sulfate and the barium salt of sulfoacetaldehyde. Upon the basis of these results the following structure was assigned.



BIBLIOGRAPHY

1. P. Baumgarten, Ber., 59, 1166, 1973 (1926).
2. F. Beilstein and E. Wiegand, Ber., 16, 1267 (1883).
3. O. W. Willcox, Am. Chem. J., 32, 450 (1904).
4. C. M. Suter, P. B. Evans and J. M. Kiefer, J. Am. Chem. Soc., 60, 538 (1938).

5. F. G. Bordwell, C. M. Suter and A. J. Webber, J. Am. Chem. Soc., 67, 827 (1945).
6. A. P. Terentyev and L. A. Kazitsina, Compt. rend. acad. sci. U.R.S.S., 51, 603 (1946).
7. A. P. Terentyev and S. K. Golubeva, ibid., 51, 689 (1946).
8. A. P. Terentyev and L. A. Kazitsina, ibid., 55, 625 (1947).
9. A. P. Terentyev and L. V. Tsymbal, ibid., 55, 833 (1947).
10. A. P. Terentyev and L. A. Kazitsina, J. Gen. Chem. U.S.S.R., 18, 723 (1948) (Engl. translation).
11. A. P. Terentyev and L. A. Kazitsina, ibid., 19, 481 (1949).
12. A. P. Terentyev and L. A. Yanovski, ibid., 19, 487 (1949).
13. A. P. Terentyev, S. K. Golybeva and L. V. Tsymbal, ibid., 19, 763 (1949).
14. A. P. Terentyev and N. P. Volynsky, ibid., 19, 767 (1949).
15. A. P. Terentyev and L. A. Yanovskaya, ibid., 19, 1367 (1949).
16. A. P. Terentyev and A. V. Dombrovsky, ibid., 19, 1469 (1949).
17. A. P. Terentyev and L. A. Kazitsina, ibid., 19, a421 (1949).
18. A. P. Terentyev and L. A. Yanovskaya, ibid., 19, a591 (1949).
19. A. P. Terentyev, L. A. Kazitsina and A. M. Turovskaya, ibid., 20, 187 (1950).
20. A. P. Terentyev, L. A. Yanovskaya and V. G. Yashunsky, ibid., 20, 539 (1950).
21. A. P. Terentyev and A. V. Dombrovsky, ibid., 21, 302 (1951).
22. A. P. Terentyev and L. A. Yanovskaya, ibid., 21, 307 (1951).
23. A. P. Terentyev and A. V. Dombrovsky, ibid., 21, 775 (1951).
24. A. P. Terentyev and L. A. Yanovskaya, ibid., 21, 1415 (1951).
25. G. Ciamician and P. Silber, Ber., 18, 879 (1885).
26. P. Pratesi, Gazz. chim. ital., 65, 43 (1935).

SYNTHESIS OF SUBSTITUTED SILANES

Reported by C. W. Hinman December 19, 1952

Introduction

Organic compounds of silicon have been known for more than a hundred years, many of them having been prepared with the expectation that they would be analogous to those of carbon. It was found, however, that silicon differs from carbon in many respects. One of these is that the silicon-oxygen bond is exceedingly strong as compared to silicon and any other element. Another is that chains having more than five consecutive silicon atoms are highly unstable and most readily subject to hydrolysis.[1] Organosilicon compounds are solely products of the laboratory, as none have been found in nature.

Synthesis

The basic starting materials for the production of organosilicon compounds is either elemental silicon or silicon tetrahalide. Elemental silicon is produced by reacting magnesium with silicon dioxide, or by reaction of an alkali metal on silicon tetrahalide. Silicon tetrachloride is produced from ferrosilicon (FeSi) and chlorine, or from free silicon and chlorine.[2]

Friedel-Craft Method

The earliest method of forming carbon-silicon bonds, the so-called Friedel-Craft Method, involved the use of zinc alkyls as indicated by the equation:

$$2ZnR_2 + SiCl_4 \xrightarrow[\text{sealed tube}]{150\text{-}200^\circ} SiR_4 + 2ZnCl_2$$

where R is either alkyl or aryl.[3] From one to four positions can be filled by controlling the molar quantities of the reagents, but even though one product predominates a mixture always results. Obvious disadvantages of the method are the sealed tube conditions, the preparation and handling of the highly flammable and toxic zinc alkyls and the separation of products. Organo disilanes have been prepared by this method also.

$$Si_2I_6 + 3Zn(C_2H_5)_2 \longrightarrow (C_2H_5)_3Si\text{-}Si(C_2H_5)_3 + 3ZnI$$ [4]

Würtz Method

Generally, the Würtz method is more versatile and gives more easily separated products.

$$SiCl_4 + 4RCl + 8Na \longrightarrow SiR_4 + 8NaCl$$

The method finds its greatest use in the preparation of tetraalkyl- and -tetraaryl-silanes, or mixtures of these two.[5]

$$(C_6H_5)_3Si\text{-}Cl + H_3CCl \xrightarrow{2Na} (C_6H_5)_3Si\text{-}CH_3 + 2NaCl$$ [6]

$$(C_2H_5O)_2SiCl_2 + 2NaC{\equiv}CH \longrightarrow (C_2H_5O)_2\text{-}Si\text{-}(C{\equiv}CH)_2$$ [7]

It cannot be applied in the case of the silane halides which contain hydrogen, because "unsaturated" non-volatile hydrides with formulas varying from SiHn to $(SiH_{1.8})_n$ are formed.[8]

Direct Method

A method which is used commercially is the direct union of alkyl or aryl halides with metallic silicon.

$$2RCl + Si \xrightarrow[150\text{-}300^{\circ}]{} R_2SiCl_2$$

This reaction is carried out in the presence of finely divided copper or silver. It has been found, that if R is alkyl, copper works best, if R is aryl silver is the most effective.[9]

Saturated Hydride Synthesis

Saturated hydride silanes are produced by allowing magnesium silicide (Mg_2Si) to drop into a liquid ammonia solution of ammonium bromide. A mixture of gases consisting of hydrogen, silane (SiH_4), disilane (Si_2H_6), and small amounts of trisilane (Si_3H_8) is produced.[10]

Grignard Synthesis

This method has found the widest use of all, especially in the laboratory, for this method provides an easy means to most of the desired organosilicon compounds in good yields.

$$3RMgX + SiCl_4 \longrightarrow R_3SiCl + 3MgX_2$$

$$3RMgX + SiHCl_3 \longrightarrow R_3SiH + 3MgX_2$$

It is difficult to prepare tetraalkyl- or tetraaryl silanes by this method, however. In cases where the Grignard method gives poor yields or fails to react it has been found that the organolithium compounds often can be used.

$$SiCl_4 + 4RLi \longrightarrow SiR_4 + 4LiCl$$

This usually gives tetrasubstituted silanes, but in some cases of sterically hindered lithium compounds only the di- or trisubstituted compounds are isolated. It should also be noted that trialkyl- and triaryl-silanes react with organolithium compounds.[11]

$$R_3SiH + RLi \longrightarrow R_4Si + LiH$$

The reactions of organosilicon Grignard reagents are very general, but for the sake of clarity only a few of the more simple ones will be given here to illustrate some of these reactions.

$$(H_3C)_3\text{-}Si\text{-}CH_2Cl \xrightarrow{Mg} (CH_3)_3Si\text{-}CH_2MgCl$$

$$(H_3C)_3\text{-}Si\text{-}CH_2MgCl + CO_2 \longrightarrow (H_3C)_3SiCH_2CO_2H$$

$$(H_3C)_3SiCH_2MgCl + H_3C\overset{O}{\overset{\|}{C}}H \longrightarrow (H_3C)_3SiCH_2CHOHCH_3$$

$$(H_3C)_3SiCH_2MgCl + (H_3CCO)_2O \longrightarrow (H_3C)_3SiCH_2COCH_3$$

$$(H_3C)_3SiCH_2MgCl + H_3CCOCH_3 \longrightarrow (H_3C)_3SiCH_2COH(CH_3)_2$$

$$(H_3C)_3SiCH_2MgCl + H_2C\overset{O}{\triangle}CH_2 \longrightarrow (H_3C)_3SiCH_2CH_2CH_2OH \quad {}^{12}$$

$$(H_3C)_3SiCH_2MgCl + (CH_3)_3SiCl \longrightarrow (H_3C)_3SiCH_2Si(CH_3)_3$$

$$(H_3C)_3SiCH_2MgCl + (CH_3)_2SiCl_2 \longrightarrow (H_3C)_3SiCH_2\text{-}\overset{CH_3}{\underset{CH_3}{Si}}\text{-}CH_2Si(CH_3)_3 \quad {}^{13}$$

$$(H_3C)_3Si\underset{C_6H_5}{C}HMgBr + (CH_3)_3Si\overset{H}{\underset{C_6H_5}{C}}Br \longrightarrow (H_3C)_3Si\text{-}\overset{H}{\underset{C_6H_5}{C}}\overset{C_6H_5}{\underset{H}{C}}\text{-}Si(CH_3)$$

$$(H_3C)_3SiCH_2MgBr + BrCH_2CH{=}CH_2 \longrightarrow (H_3C)_3SiCH_2CH_2CH{=}CH_2 \quad {}^{14}$$

$$H_3C(CH_2)_2C{\equiv}CMgBr + (CH_3)_3SiCl \longrightarrow H_3C(CH_2)_2C{\equiv}CSi(CH_3)_3$$

$$BrMgC{\equiv}CMgBr + 2(CH_3)_3SiCl \longrightarrow (H_3C)_3SiC{\equiv}CSi(CH_3)_3 \quad {}^{15}$$

BIBLIOGRAPHY

1. H. Hausman, J. Chem. Ed. 23, 16 (1946).
2. T. Alfrey, F. Honn, and H. Mark, J. Polymer Chem. 1, 102 (1946).
3. Aldrich, Organic Seminar Abstracts, January 23, 1948.
4. Friedel, Compt. Rend. 68, 923 (1869).
5. Gilman and Clark, J. Am. Chem. Soc. 68, 1675 (1946).
6. Bygen, Ber. 48, 1236 (1915).
7. Frisch and Young, J. Am. Chem. Soc. 74, 4853 (1952).
8. A. Stock et.al. Ber. 54, 524 (1921); 56, 1698 (1923).
9. E. G. Rockow, J. Am. Chem. Soc. 67, 963 (1945).
10. Johnson and Hogness, J. Am. Chem. Soc. 56, 1252 (1934).
11. W. H. Hill, Jr., Organic Seminar Abstracts, November 19, 1948.
12. Hauser and Hance, J. Am. Chem. Soc. 74, 5091 (1952).
13. Whitmore et.al. J. Am. Chem. Soc. 70, 4184 (1948).
14. Hauser and Hance, J. Am. Chem. Soc. 74, 5091 (1952).
15. Frisch and Young, J. Am. Chem. Soc. 74, 4853 (1952).

RING CONTRACTION REACTIONS OF TROPOLONES

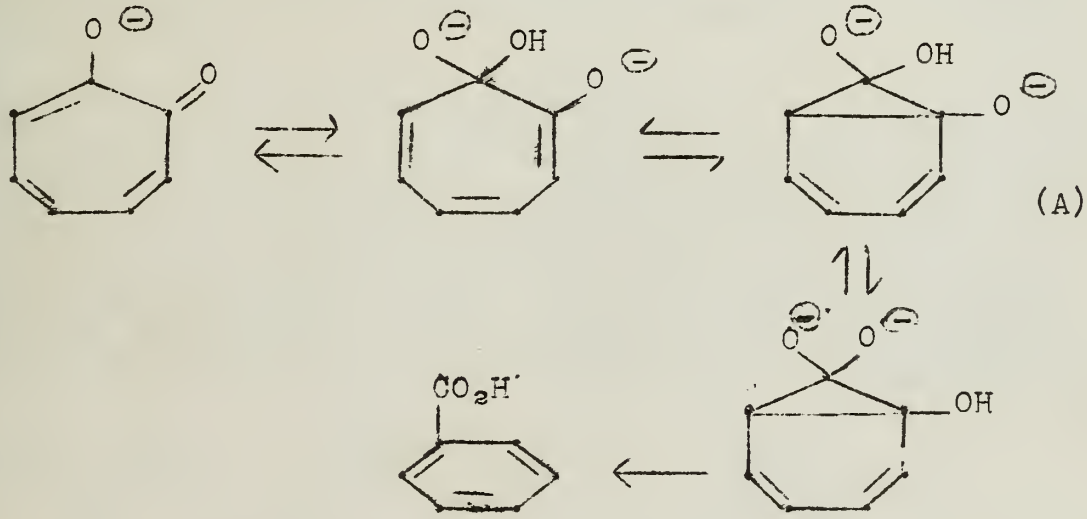
Reported by Harry W. Johnson, Jr. December 19, 1952

Among the more interesting reactions which the tropolones and substituted tropones undergo are those which lead to the formation of benzenoid products. Four such reactions will be discussed here: A) the base induced reactions of tropolones, tropolone ethers and 2-halotropones; B) the reaction of tropolone with hypohalite; C) the ring contraction encountered with 3- and 7-diazotropolones; and D) the contraction of polynitrotropolones under acidic or neutral conditions.

A. <u>The base induced reaction</u>

Tropolone, when heated to 230-235° in the presence of KOH, undergoes rearrangement to yield benzoic acid (17%).[1] Many such reactions of tropolones are known, and they have been used in the establishment of the structures of substituted tropolones.[1,2,3] Equation (I) illustrates the commonly asserted mechanism for such reactions.

(I)

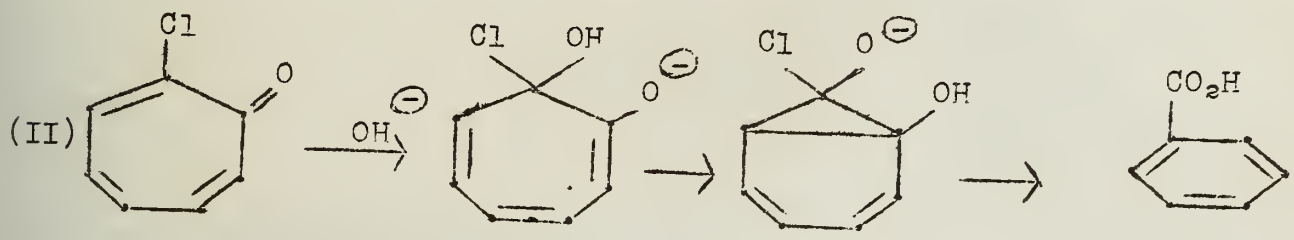


Included in the above reaction sequence are intermediates of the norcaradiene type; and, while no substance has been shown to have the norcaradiene skeleton (eg. A), there is evidence that cycloheptatriene is in equilibrium with norcaradiene as shown by the formation of a Diels Alder adduct derived from B.[4]

(B)

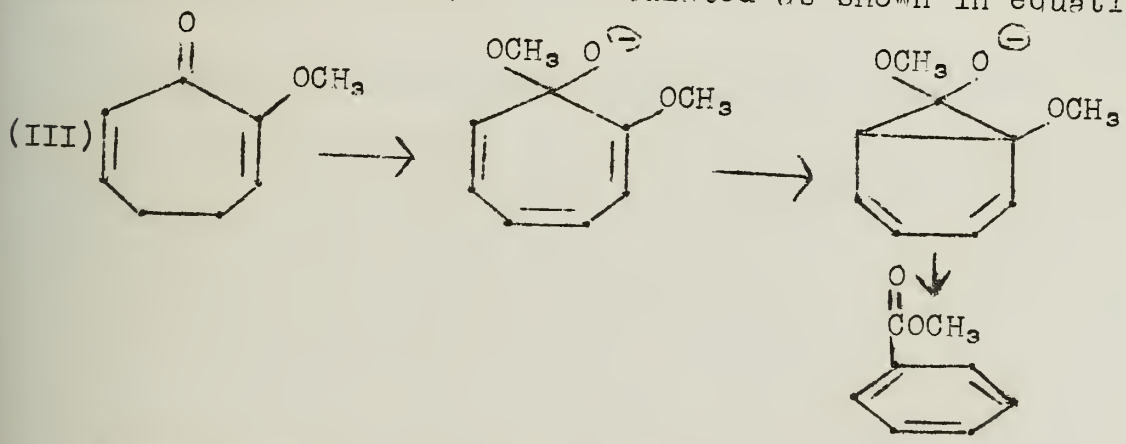
The 2-halotropones also undergo ring contraction with hydroxide ion, but the conditions required are much milder. 2-chlorotropone may be rearranged by heating it under reflux with 3 <u>N</u>

sodium hydroxide for 2 hours (70% yield),[5,6] while the 2-bromo- and 2-iodotropones undergo rearrangement when heated at 100° with 1 N sodium hydroxide for an hour in yields of 42 and 52%, respectively, after purification.[7] The 2-halotropones do not, however, undergo ring contraction when trated with bases other than hydroxide; with these (e.g. ammonia, methoxide, phenyllithium, or phenylmagnesium bromide)[6,7] the usual reaction is displacement. The mechanism below (II) is consistant with the above facts.



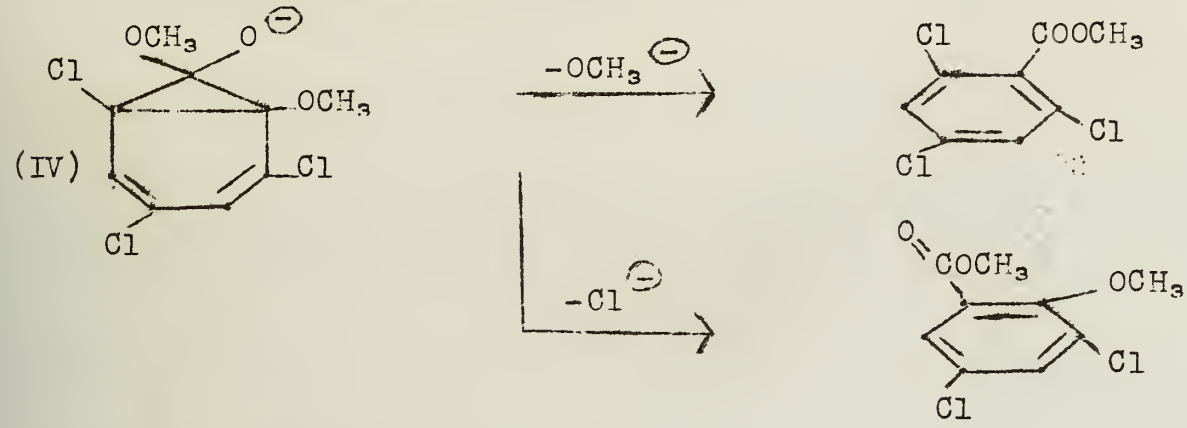
It will be noted that in equation (II) one of the essential features is the transfer of the proton to the leaving hydroxyl group. In the bases other than hydroxyl which were noted above, the proton is unlikely to be available for transfer, so that displacement is favored.

Ring contraction is also to be found in the tropolone ethers; here, however, methoxide is the base of choice, since hydroxide results in hydrolysis of the ether.[1] Tropolone methyl ether, when treated with sodium methoxide in refluxing methanol, yields methyl benzoate (46% on basis of benzoic acid obtained on saponification),[1,3] as do the substituted ethers (see, however, the next paragraph on halotropolone ethers). In this case attack at the carbon bearing the methoxyl group is fruitless for rearrangement so attack at the carbonyl is postulated as shown in equation (III).



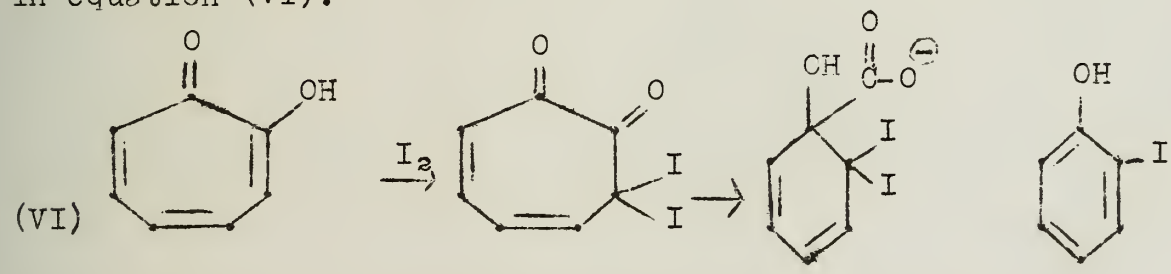
Compounds such as 3,5,7-trichlorotropolone methyl ether have been studied,[5,8] and it was found that on treatment with sodium methoxide in refluxing methanol there were formed 79% methyl 2,4,6-trichloro benzoate and 19% 2-methoxy-3,5-dichlorobenzoic acid. In this case the compound may react either as a halotropone (normally giving displacement) or a tropolone methyl ether (normally giving rearrangement). It is apparent that the compound reacts as an

ether, but since the following species (IV) is in the reaction sequence, either halide or methoxide may be eliminated.



B. Ring contraction with hypohalite

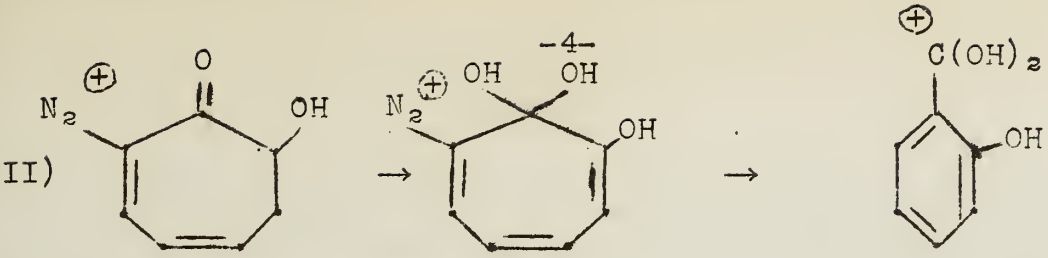
If tropolone is allowed to stand at room temperature with 2 N sodium hydroxide containg 2 molar equivalents of iodine or bromine, triiodo- or tribromophenol is obtained in yields of 20 or 30%,[1,5] respectively. The mildness of the conditions, as compared with those required when sodium hydroxide alone is used, led to the postulation of a different mechanism, in which the halogen plays an essential part, for the reaction.[1] The mechanism is illustrated in equation (VI).



C. Formation of salicylic acids via diazonium salts

In attempts to make 3- or 7-halo or cyano tropolones, several authors tried to use the Sandmeyer reaction on the 3- or 7-amino-tropolones. In such cases one usually obtains a mixture of the Sandmeyer product and salicylic acid.[2,3,9] For example, 7-amino-4-isopropyl-tropolone, when diazotized and subjected to the Sandmeyer reaction, yields 3- and 7-isopropyltropolone together with 25-30% of p-isopropyl-salicylic acid.[9] The salicylic acid is obtained in yields of 50-60% if the diazonium salt is heated with dilute sulfuric acid.[9,10] The following mechanism has been postulated to account for the reaction. It should, perhaps, be noted that the diazonium salts do not undergo immediate rearrangement, since Haworth has demonstrated that it is possible to couple the diazonium salt from 2-amino-6-methyltropolone with the sodium salt of β-napthol.[2]

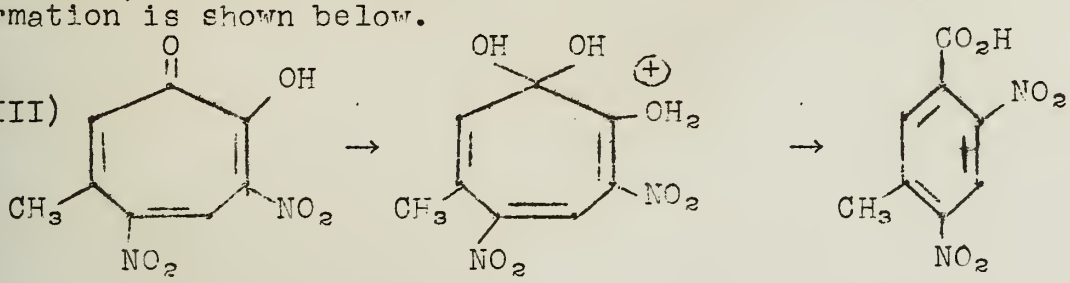
(VII)



D. Acid catalyzed rearrangements of troponones

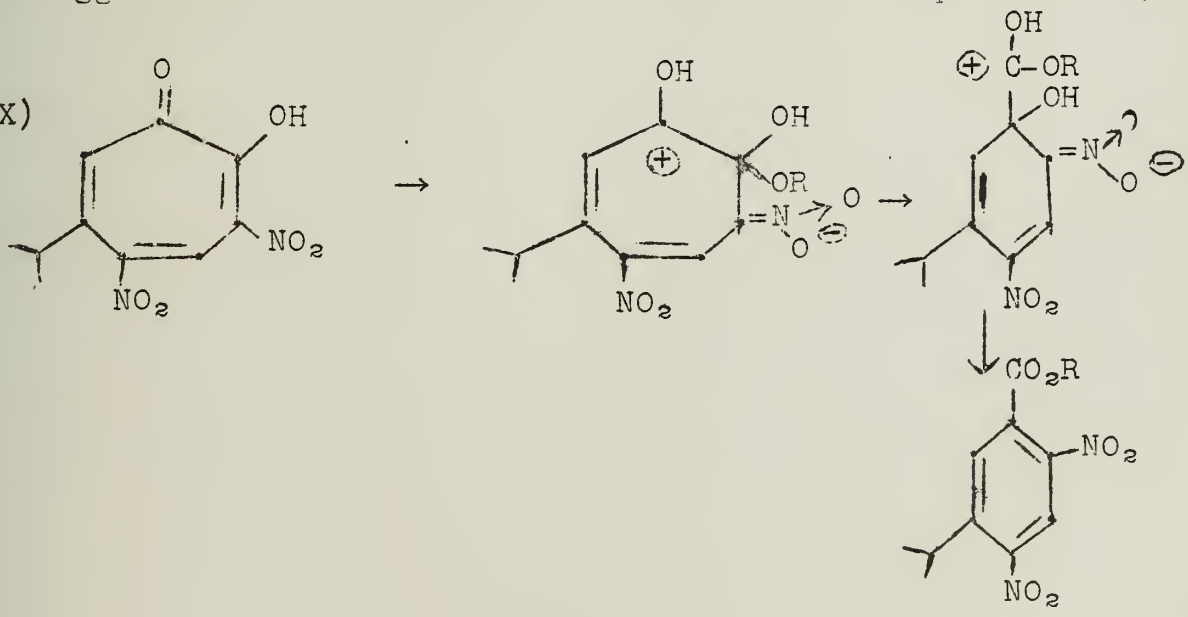
The nitration of 6-methyltropolone yields a complex mixture of mono-, di-, and trinitrotropolones, together with some (yields not stated) 4,6-dinitro-m-toluic acid.[2] The route suggested for its formation is shown below.

(VIII)



In another polynitrotropolone (3,5-dinitro-6-isopropyltropolone) it was noted that rearrangement to the dinitro benzoate occured when heated for a few moments in methyl or ethyl alcohol. The suggested course of the reaction is shown in equation (IX).[3,10]

(IX)



BIBLIOGRAPHY

1. W. von E. Doering and L. H. Knox, J. Am. Chem. Soc., 73, 828 (1951).
2. R. D. Haworth and P. R. Jeffries, J. Chem. Soc., 2067 (1951).
3. A. J. Birch, Ann. Rpts., XLVIII, 185 (1951).
4. E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, J. Am. Chem. Soc., 61, 1057 (1939).
5. W. von E. Doering and L. H. Knox, J. Am. Chem. Soc., 74, 5683 (1952).

6. B. J. Abdir, J. W. Cook, J. D. Loudon, D. K. V. Steel, J. Chem. Soc., 2850 (1952).
7. W. von E. Doering and L. H. Knox, J. Am. Chem. Soc., 74, 5688 (1952).
8. J. W. Cook, R. M. Gibb and R. A. Raphael, J. Chem. Soc. 2244 (1951).
9. T. Nozoe, Y. Kitahara, and K. Doi, J. Am. Chem. Soc., 73, 1895 (1951).
10. T. Nozoe, Nature, 167, 1055 (1951).

CONCERTED REACTIONS: POLYFUNCTIONAL CATALYSTS

Reported by Richard L. Johnson January 9, 1952

In organic chemistry there are two main classes of reactions, ionic and free radical reactions. The polar displacements are generally regarded as falling between two extremes: S_N1 and S_N2 reactions, according to their apparent kinetic order in aqueous or other polar solvents. Swain[1,2] has shown that both extreme cases display third order kinetics in nonpolar solvents such as benzene.

The principle that both electrophilic and nucleophilic reagents are necessary for a polar chemical reaction is supported by the observations that no polar reactions have been found to occur in the gaseous phase, all reaction taking place on the container or catalyst provided. Swain's direct evidence was procured through experiments in benzene solution with pyridine and methyl bromide[3] (for S_N2 type) and with triphenylmethyl halides and methanol[4] (for S_N1 type).

In aqueous solution the kinetics of the enolization of acetone and the mutarotation of glucose (apparently first order in reactant and hydronium ion in acidic solution and first order in reactant and hydroxyl ion in basic solution) were shown to be explainable on the basis of a termolecular reaction.[5] The nucleophilic reagent may be OH^- or RCO_2^- in basic solution and H_2O in acidic solution. The electrophilic reagent may be H_2O in basic solution and H_3O^+ or RCO_2H in acidic solution. Since water is present in the same constant high concentration with respect to the other reagents, the third order term is not experimentally detectable in the mutarotation of glucose in aqueous solution.

In ordinary reactions the nucleophylic, electrophilic, and reacting groups are in separate molecules (Fig. 1). If the nucleophilic group is in the same molecule as the reacting species, the neighboring group reactions, studied by Winstein, occur (Fig. 2). The unusually high reactivity of tetramethylene glycol toward HBr in phenol may be explained as an example in which the electrophilic and reacting groups are in the same molecule (Fig. 3). If the nucleophilic and electrophilic groups are present in the same catalyst molecule, polyfunctional catalysis can occur (Fig. 4).

Figure 1

Figure 2

Figure 3

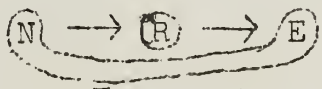


Figure 4

When two functional groups are available in the same molecule, only a bimolecular collision is necessary to effect a reaction (Figs. 2, 3, 4); therefore the rate is increased. This situation is

especially advantageous in dilute solutions where termolecular collisions are rare in relation to bimolecular ones.

The mutarotation of tetramethyl glucose in non-aqueous solutions provides an interesting example of acid-base catalysis. Prior to 1927, T. M. Lowry[6,7,8] had shown that the mutarotation reaction requires both an acidic (electrophilic) and a basic (nucleophilic) catalyst for the formation of the free aldehyde from the hemiacetal. The recyclization of the aldehyde occurs at a faster rate than the opening, hence does not effect the overall rate. In inert (aprotic) solvents, such as chloroform, the reaction proceeded at a slow rate. In the dryest benzene that Lowry could prepare, the rate was also slow, and it increased more than a hundredfold when a trace of water was added. In ethyl acetate, where the rate was again slow, the addition of a trace of water was not so effective, because the water was more tightly bound to the ester than to the benzene, reducing the catalytic activity. Pyridine alone was a poor catalyst, but a mixture of pyridine and water in the ratio two to one was twenty times as effective. Dry cresol likewise gave no appreciable catalysis alone, but one to two mixtures of pyridine and cresol had a rate twenty times as fast. That the polarity or the dielectric constant of the aprotic solvent was not an important factor was shown by the demonstration that ethyl acetate and acetone retarded, rather than speeded, the reaction. The salts of strong acids were found not to catalyze the reaction, although undissociated weak acids and bases did catalyze it.

Lowry's work definitely established that mutarotation required both acidic and basic catalysts. Until Swain's work, it was thought that there were two different mechanisms for the reaction, one operating in acidic media, the other in basic media. Both mechanisms led to a common intermediate, through the action of first one species of catalyst, then the other, and no reaction step involved more than a bimolecular collision. Other, more complex, mechanisms of this type have been considered, but none involves a step of more than second order.

The concerted mechanism[9] shows the reaction proceeding by a simultaneous attack of acidic and basic catalysts in a termolecular reaction as shown in Figure 5.

Figure 5

Swain and Brown[9] repeated the work of Lowry, with the difference that they ran the reactions in benzene solutions instead of running them without solvent. Because the concentration of the catalysts

did not change during the reaction, the kinetic order of each run was first order. The variation of the rate of reaction caused by varying the amounts of the catalysts was used to determine the true order of the reaction. The total rate expression for mixtures of phenol and pyridine was found to be:

$$k = 0.0000013 + 0.0081\ (\phi OH)^3 + 0.00048\ (Py)\ (S + S')$$
$$+ 0.21\ (Py)\ (\phi OH) + 0.84\ (Py)\ (\phi OH)^2$$

where the first term is the "blank" (rate in pure benzene) term, the second concerns catalysis by phenol and a phenol dimer, the third shows action of pyridine as base and sugar as acid, [(S + S') representing total sugar concentration, both α and β forms], the fourth term represents the action of phenol as acid and pyridine as base, and the last, which is appreciable only in concentrated solutions, shows the action of a phenol dimer as acid with pyridine as base. The need to include the sugar in an "acid catalysis" term shows that the sugar itself may act as an acid in this reaction, but not as a base.

All except the "blank" term are at least third order when sugar concentration is considered. The results of these experiments indicate that the mutarotation of tetramethyl glucose is indeed a termolecular reaction requiring both acidic and basic catalysts. The equation is in substantial agreement with the data of Lowry and Falkner.[6] 2-4-Dinitrophenol and p-nitrophenol gave much faster rates than phenol when pyridine was added, but not enough data were gathered to show the kinetic order of the reaction. The catalytic effect of 3-hydroxyquinoline was tested in acetone rather than benzene because of the low solubility of this catalyst in benzene. Acetone alone caused no catalysis, and the reaction constant was first order in sugar and second order in catalyst, indicating that one molecule of the catalyst acted as a base, another as an acid.

In the latest paper in this series[10], Swain and Brown have shown the existence of bifunctional catalysts for the mutarotation reaction. These catalysts have both acidic and basic groups so situated that one molecule of the catalyst can simultaneously donate one proton and remove another from the glucose molecule. When this situation occurs, it is necessary for only one molecule of catalyst to become associated with the reacting molecule to make the reaction possible; hence in non-polar solvents the reaction will obey second order kinetics.

The polyfunctional catalyst most studied was 2-hydroxypyridine. It is only 1/1000 as strong a base as pyridine, and only 1/100 as strong an acid as phenol, but it is found to be a very much stronger catalyst than both, as shown in the table below:

Conc. 2-OH Py	Conc. each of Py and ØOH	Relative effectiveness of 2-OH Pyridine
0.05 M	0.05 M	50 times better
0.001 M	0.01 M (Calculated Rate)	7000 times better

Despite the fact that it is a nearly neutral molecule, the 2-hydroxypyridine is over ten times as effective in benzene as hydronium ion is in water. With 0.001 M catalyst, the rate is not significantly changed by the addition of either 0.1 M phenol or 0.1 M pyridine, showing that the polyfunctional catalyst is self-contained.

3- and 4-Hydroxypyridine are at least as reactive as the 2-hydroxypyridine in ordinary reactions. The two functional groups are, however , too far apart to react simultaneously with the sugar molecule. These substances are less than 1/1000 as effective as the 2-hydroxypyridine, and the kinetic order of the rate determining step is third order, showing that two molecules of catalyst are needed per sugar molecule.

The 2-hydroxypyridine and the sugar form a complex immediately upon mixing, as evidenced by an increase in optical rotation of the solution. Neither of these substances complexes with either phenol or pyridine. The complex formed is probably a chelate, shown in Figures 6 and 7. Which form of the catalyst predominates in benzene solution is unknown. The catalyst is found to complex also with 2-tetrahydropyranol, (Fig.8), which thereby inhibits the mutarotation of the sugar.

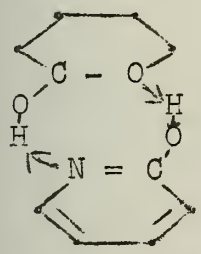


Figure 6

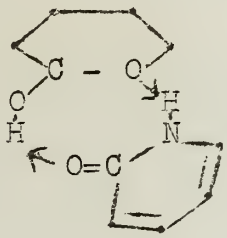


Figure 7

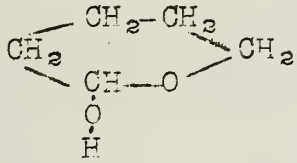


Figure 8

From the kinetic data it appears that other catalysts for the reaction are: (in benzene solution)

Polyfunctional	Acidic only	Basic only
2-hydroxy-4-methylquinoline	p-nitrophenol	pyridine
Benzoic Acid	phenol	2-methoxypyridine
Picric Acid		N-methyl α-pyridone
2-aminopyridine		

In benzene solution the rate constant for 2-hydroxypyridine catalysis is half order in catalyst in concentrated solution, increasing to first order in very dilute solutions. In such solutions the sugar approaches zero order kinetically.

Chlorobenzene and acetone solutions gave like results to benzene solutions. In water solutions, glucose itself was used as the reactant since its rate of mutarotation is about the same as that of tetramethyl glucose. 2-Hydroxypyridine was four to five times as effective as the calculations predicted on the basis of its acid-base constants as a monofunctional catalyst. This rate is not nearly so spectacular as that in non-aqueous media.

The work of Swain and Brown shows that a polyfunctional catalyst must have both acidic and basic groups so arranged that they will

possess a pattern of polarities opposite to that of the reacting species in the transition state. The resemblance between polyfunctional catalysts and enzymes becomes apparent at once. They have these characteristics in common:

1. They possess no extremely reactive functional groups.
2. They have high activity in dilute concentrations at mild temperatures and in nearly neutral solutions.
3. They are specific.
4. They form complexes with the reacting molecule before reaction occurs.
5. They react by polar, rather than free radical, reactions.

The probability that enzymes react as polyfunctional catalysts in concerted displacements is supported by the observations that enzyme-catalyzed reactions have low activation energies, as could be achieved through polyfunctional catalysts. It is interesting to note that an enzyme has been discovered which catalyzes the mutarotation of glucose at a rate 20 times that of hydroxyl ion.[11]

REFERENCES

1. See: A. Kresge, Organic Seminars, U. of Ill., I Semester, 1950
2. C. G. Swain, Record of Chemical Progress, 12, 21, (1951)
3. C. G. Swain, et al., J. Am. Chem. Soc., 70, 1119, (1948)
4. C. G. Swain, et al., ibid. 70, 2989, (1948)
5. C. G. Swain, et al., ibid. 72, 4578, (1950)
6. T. M. Lowry, J. Chem. Soc., 127, 1383, (1925)
7. T. M. Lowry, et al., ibid, 127, 2883, (1925)
8. T. M. Lowry, et al., ibid., 2539, (1927)
9. C. G. Swain and J. F. Brown, J. Am. Chem. Soc., 74, 2534, (1952)
10. C. G. Swain and J. F. Brown, J. Am. Chem. Soc. 74, 2538, (1952)
11. D. Keilin and E. F. Hartree, Biochem. J., 50, 341, (1952)

SOME METHODS OF STEPWISE PEPTIDE DEGRADATION

Reported by N. W. Kalenda January 9, 1953

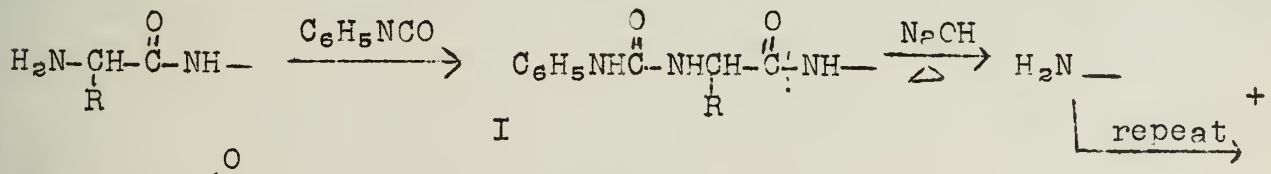
Peptides are relatively low molecular weight polyamides formed from α-amino acids. Proteins, the most important of all organic compounds, are essentially large peptides. In order to analyze the structures of compounds belonging to this latter class of substances, methods must be used which will permit the determination of the exact sequence of the α-amino acids.

Two general procedures for determining the structure of peptides are available. One procedure[1] involves the cleavage of the peptide chain into smaller fragments, the separation and identification of these fragments, and the reconstruction of the ch chain from the information obtained. This method has been exploited with striking success by Sanger in his work on insulin.[2] The other procedure involves the stepwise removal of amino acids from the peptide chain. Most of the methods in this procedure make use of the driving force of a ring closure to eliminate the terminal amino acid.

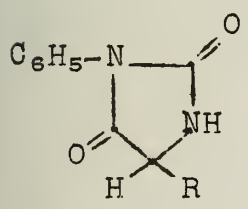
For the stepwise procedure, the degradation may be directed at either the free α-amino or the free carboxyl[3-7] end of the molecule. Methods involving the former will be considered in this seminar.

The methods to be considered have as their ultimate goal the degradation of naturally occurring proteins. At present, however, the methods are being tested on simpler compounds -- synthetic peptides.

The earliest method developed[8,9] involves the treatment of the peptide with phenylisocyanate to form a phenylureide (I) and the cleavage of the phenylureide to a hydantoin (II) and a peptide residue. The hydantoins are easily separated and identified by elementary analysis and by comparison with authentic samples. The yields are good; the tripeptide alanylglycylleucine coupled in an almost quantitative yield and gave a hydantoin in a yield of 96%.



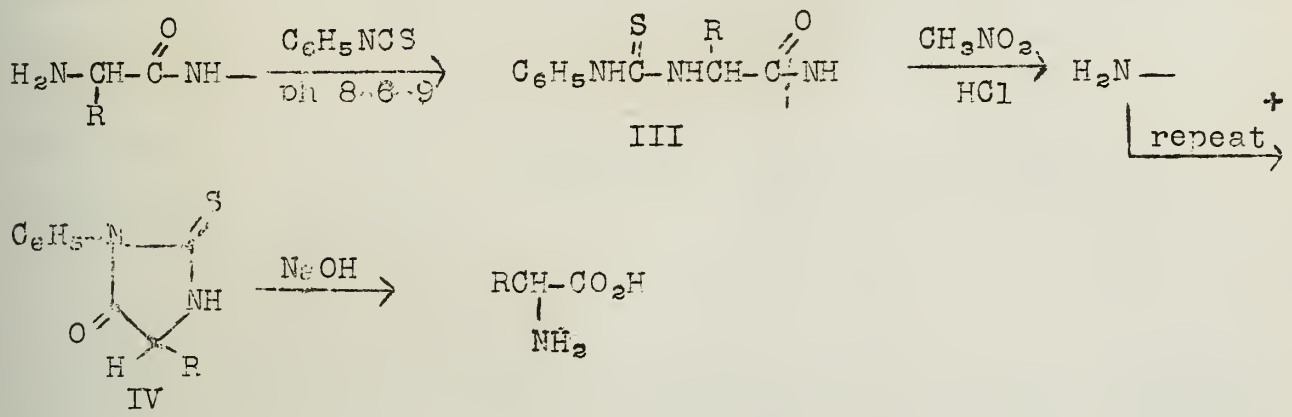
I



II

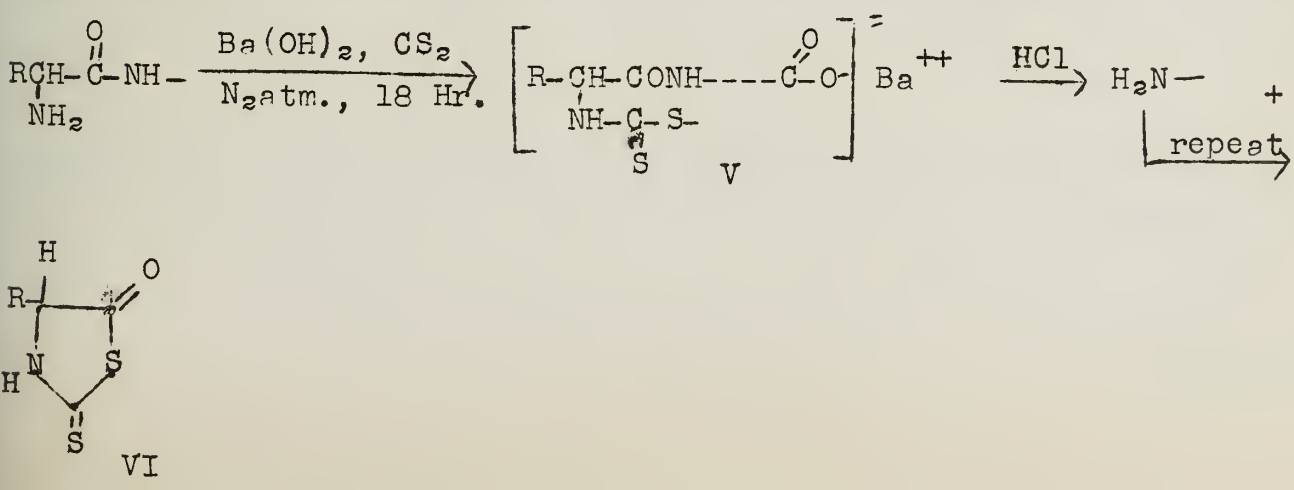
The general utility of this method is limited by the fact that the bigorous hydrolysis procedure splits the peptide bonds to a small but definite extent.

In order to overcome the chief obstacle to the phenylisocyanate method - a small amount of hydrolysis of other peptide linkages during the formation of (II) - Edman employed phenylisothiocyanate.[10,11] The thioureido derivative (III) forms a hydantoin (IV) under milder conditions. The reaction is extremely rapid, even at room temperature, and is unaccompanied by the cleavage of other peptide linkages. The thiohydantoin is cleaved by alkaline hydrolysis and the resulting amino acid is determined by paper-strip chromatography. The method has been made microanalytical and requires only about 10 mg. of amino acid per peptide bond.

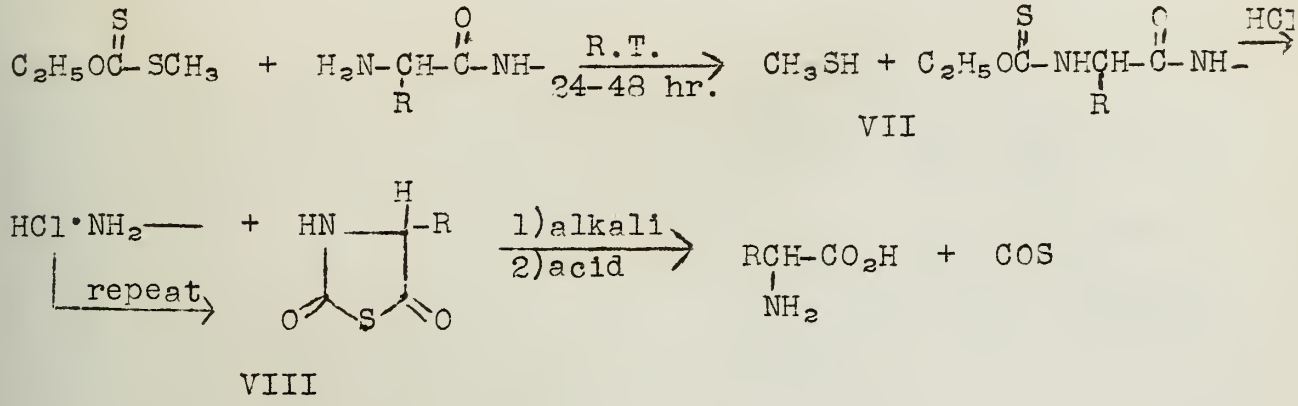


Deviations occur in the hydrolysis of the hydantoins formed from arginine, asparagaine, and tryptophane. Arginine gives rise to two ninhydrin-positive compounds, one being ornithine and the other being unidentified; asparagine gives aspartic acid; tryptophane gives two spots, the more intense of which is tryptophane. Preliminary attempts to prepare phenylthiohydantoins from the amino acids serine, threonine, and cystine show that compounds are obtained which correspond to the phenylthiohydantoins minus the elements of water in the cases of serine and threonine and hydrogen sulfide in the case of cystine;[12] these cases are being investigated further.

A method investigated by Levy[13] is the treatment of a peptide with carbon disulfide and barium hydroxide and the cleavage of the product (V) to a 2-thio-2,5-thiazolidinedione (VI). Levy has tried this method on a few di- and tripeptides. The possibility of using this method on higher polypeptides is being investigated.

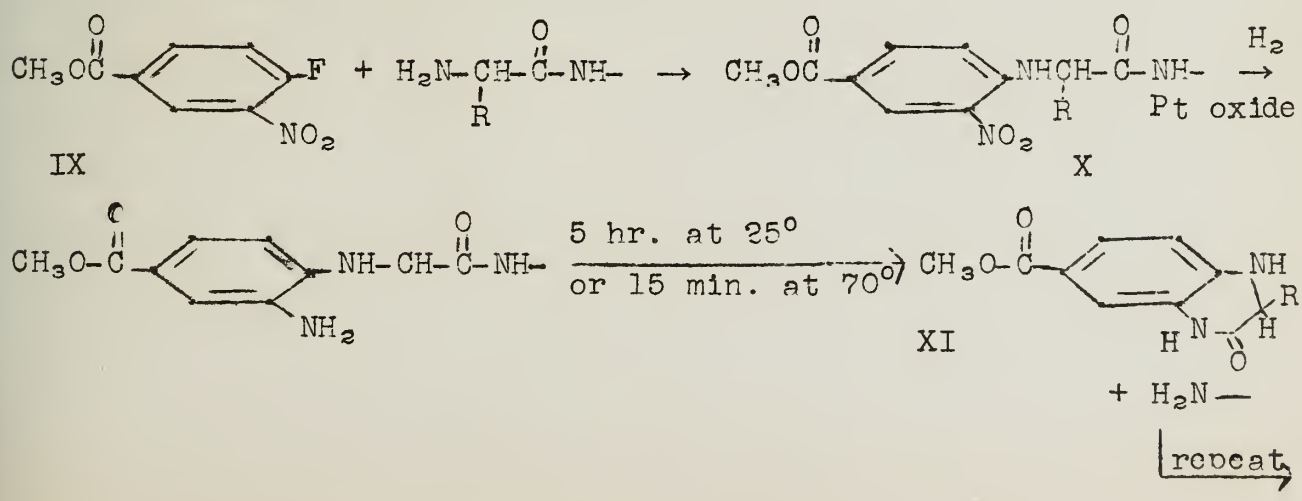


Khorana[14,15] has found that a peptide can be treated with methyl ethylxanthate to form an N(thionocarbethoxy) peptide (VII) which then is extracted from the reaction mixture and cleaved to form a 2,5-thiazolidinedione (VIII). The thiazolidinedione is cleaved to give the amino acid which is identified by paper-strip chromatography. Experiments with some di- and tripeptides have proved promising and the yields of (VIII) obtained from them were quantitative.



The method appears to offer some advantages over those developed by Levy and by Edman. Levy carried out the formation of intermediate (V) and cleavage to (VI) in the same solution, thus risking contamination of the degraded peptide with the original one, while Khorana extracted his intermediate (VII) from the reaction mixture before cleaving it. In Erdman's method, carefully controlled conditions are necessary.

A method which has proved very promising has been developed by Holley and Holley.[16] The reagent 4-carbomethoxy-2-nitrofluorobenzene (IX) reacts with peptides to form an N(4-carbomethoxy-2-nitrophenyl) peptide (X); the nitro group of (X) is reduced catalytically and the end amino acid splits off with ring closure to form a dihydroquinoxalone (XI). The average yield of (XI) per amino acid residue is 84%. The dihydroquinoxalones are crystalline compounds and are identified by comparison with samples prepared independently from (IX) and authentic amino acids.



Problems which still remain to be investigated are (I) modification of the method for peptides containing cysteine, cystine, or methionine to take care of catalyst poisoning and (2) side reacti ns occurring between (IX) and functional groups other than the terminal α-amino group.

BIBLIOGRAPHY

1. S. W. Fox, Adv. Protein Chem. 2, 155 (1945).
2. F. Sanger and H. Tupp, Biochem. J. 49, 463 (1951).
3. P. Schlack and W. Kumpf, Z. Physiol. Chem. 154, 125 (1926).
4. J. Watson and S. G. Waley, J. Chem. Soc., 2394 (1951).
5. M. Bergmann, Science 79, 439 (1934).
6. M. Bergmann and L. Zervas, J. Biol. Chem. 113, 341 (1936).
7. H. G. Khorana, J. Chem. Soc., 2081 (1952).
8. M. Bergmann, A. Miekeley, and E. Kann, Ann. 458, 56 (1927).
9. E. Abderhalden and H. Brockmann, Biochem. Z. 225, 386 (1930).
10. P. Edman, Arch. Biochem. 22, 475 (1949).
11. P. Edman, Acta Chem. Scand. 4, 283 (1950).
12. P. Edman, ibid., 4, 277 (1950).
13. A. L. Levy, J. Chem. Soc., 404 (1950).
14. H. G. Khorana, Chemistry and Industry, 129 (1951).
15. G. W. Kenner and H. G. Khorana, J. Chem. Soc., 2076 (1952).
16. R. W. Holley and A. D. Holley, J. Am. Chem. Soc. 79, 5445 (1952).

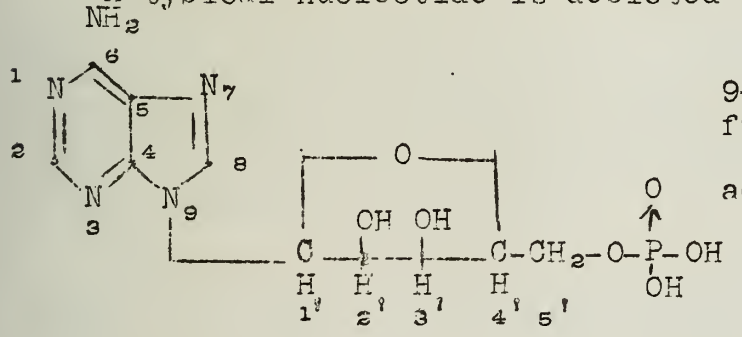
PHOSPHATE ESTERS OF NUCLEOSIDES

Reported by James C. Kauer January 9, 1953

Nucleosides are molecules composed of a monosaccharide linked by a glycosidic bond to a nitrogen atom of a nitrogenous base (generally a purine or pyrimidine derivative). The phosphate esters of these compounds are frequently called nucleotides. This seminar will deal primarily with the recent work of A. R. Todd and coworkers at Cambridge University.

Nucleotides are found in all living cells. They form complex polymeric structures called nucleic acids in which the individual nucleosides are linked by esterification with phosphoric acid. Nucleotides also form part of the structure of many coenzymes which play an important part in cell metabolism.

A typical nucleotide is depicted below.

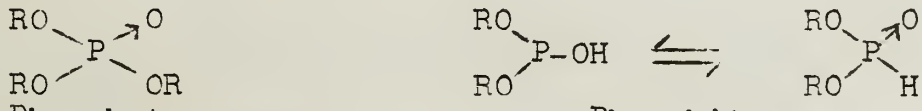


adenylic acid (I)
or
9-adenine-5'-phospho-β-D-ribofuranoside
or
adenosine-5'-phosphate

Early work by Todd and others was directed toward synthesis of the nitrogenous bases and the nucleosides. Recent work has dealt with phosphorylation of the nucleosides and linking of the resulting esters through their phosphate groups.

Phosphorus Oxy-acid Chemistry

Phosphorus forms two oxy-acids whose esters are of importance in the synthesis of nucleotides.[1]



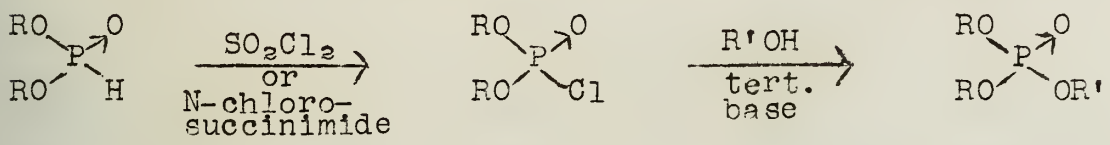
Phosphates Phosphites

The most useful syntheses of these esters are reaction of phosphate salts with organic halides and reaction of phosphorus halides with alcohols.[2]

Acyl halides react with phosphate salts to form mixed anhydrides. Pyrophosphates (diphosphates or phosphoric anhydrides) can be formed by reacting a phosphorous oxyhalide with a silver salt of phosphoric acid.

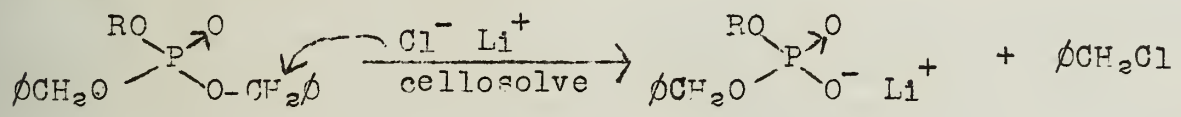
chlorophosphonate pyrophosphate

Halogenation of the phosphites yields phosphonates which Todd found to be very valuable phosphorylating agents.[2,3]



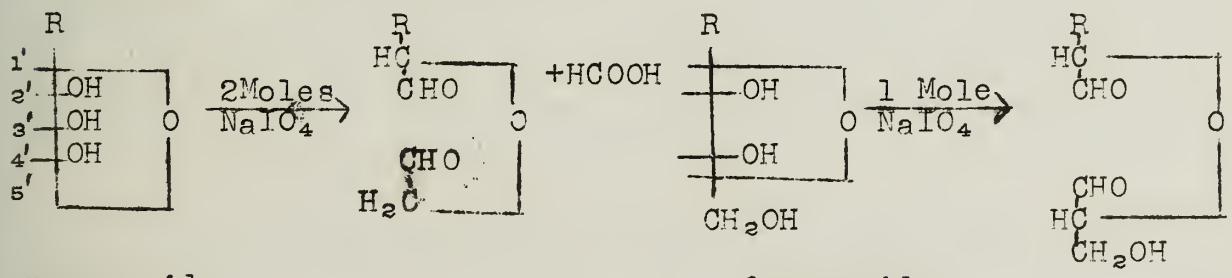
Although SO_2Cl_2 readily chlorinates the phosphite, the hydrogen chloride produced tends to rupture the nucleoside residue. For this reason, N-chlorosuccinimide gives much better results.[4]

To prevent the formation of byproducts Todd found it desirable to protect all but one of the free phosphate hydroxyls with benzyl groups which could be removed by hydrolysis or hydrogenolysis. Hydrogenolysis is preferable because nucleotides are readily destroyed by hydrolysis. He also found that tertiary bases or lithium chloride would selectively remove only one benzyl group. An S_N2 mechanism was proposed.



Structure and Synthesis of Nucleotides

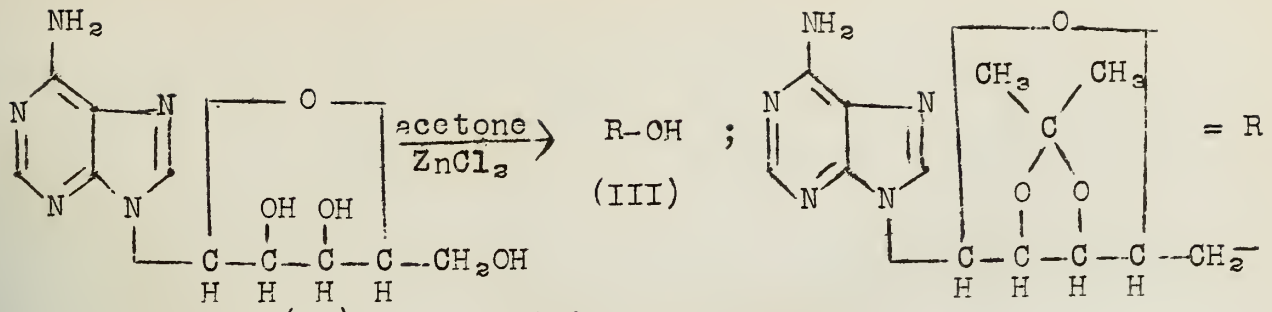
All three of the possible monophosphate esters of adenosine have been isolated from natural sources. The 5'-phosphate can be differentiated from the others by degradative studies or by periodate oxidation.[7] This latter technique, developed by Todd was also useful in verifying the fact that ribose nucleosides are furanosides and not pyranosides.[8]



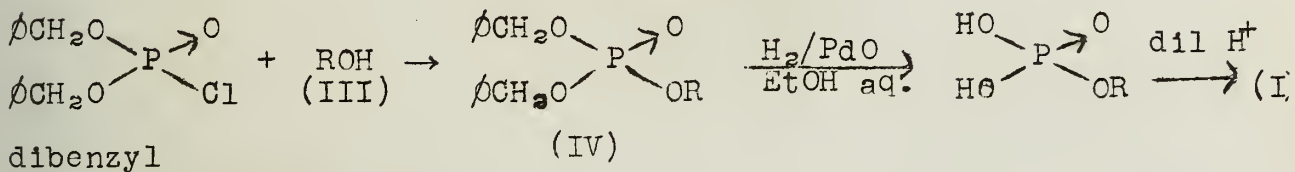
pyranoside furanoside

The 2'- and 3'-monophosphates are stable to periodate while the 5'-phosphate is oxidized.

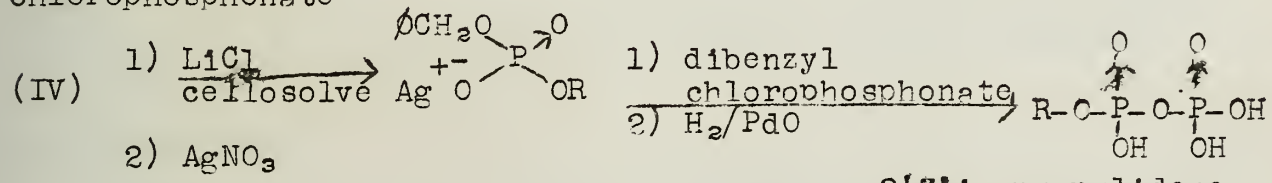
Adenylic acid and adenosine diphosphate (ADP) were among the first nucleotides to be synthesized in reasonable yield.[9,10,11]



adenosine (II) 2',3'-isopropylidene adenosine



dibenzyl chlorophosphonate (IV)

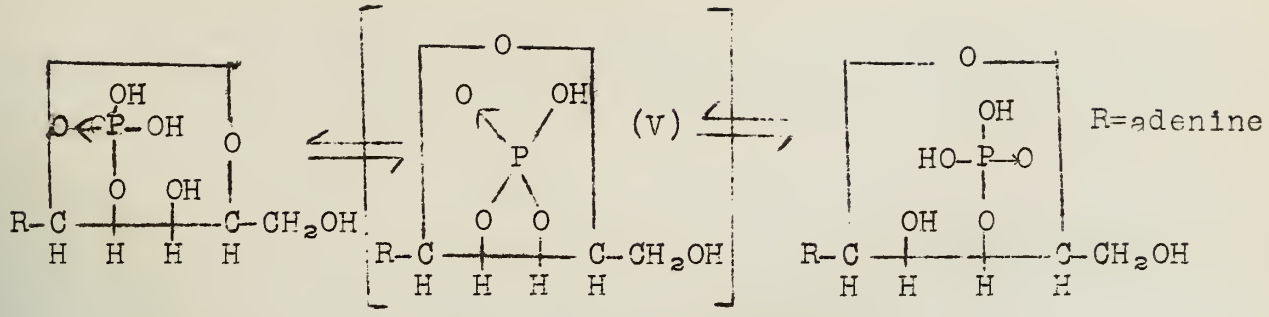


2',3'-isopropylidene adenosine-5-pyrophosphate

The 2' and 3' hydroxyls of adenosine (II) are protected by reaction with acetone. The 5' hydroxyl is phosphorylated with dibenzyl chlorophosphonate. Hydrogenolysis removes the benzyl groups, and hydrolysis removes the 2',3'-isopropylidene residue to produce adenosine-5'-phosphate (I). Monodebenzylation of (IV) followed by phosphorylation produces the tribenzyl pyrophosphate. Removal of the protecting groups gives adenosine-5-pyrophosphate (ADP).

Because of some inaccurate laboratory work,[14] it was believed for some time that the 2', 3', and 5' phosphates had been unambiguously synthesized.[7,13] It was believed that benzaldehyde formed a cyclic acetal with the 3' and 5' hydroxyls of ribose nucleosides. (Benzaldehyde is known to produce 1,3-cyclic acetals with many carbohydrates.)[15] The product of phosphorylation of this supposed 3',5'-benzylidene derivative was assumed to be the 2'-phosphate. Later work showed that the 2',3'-benzylidene nucleoside is produced, and that phosphorylation gives the 5'-phosphate.

Carter and Cohn[16] isolated two isomeric adenosine phosphates (a) and (b) from nucleic acid hydrolysates which were shown to equilibriate in acid solution.[7] Both were oxidized by periodate. It was proposed that these two acids were the 2' and 3' phosphates, and that the interconversion was analogous to that observed in the monophosphates of glycerol.



The cyclic intermediate (V) was later synthesized and was shown to be hydrolyzed into the observed mixture of (a) and (b).[18] To date no reliable general method for determining which isomer is the 2' or 3'phosphate has been worked out. It has recently been reported that by a study of the solution densities and dissociation constants of the cytidylic acids (a) and (b) the structure cytidine-3-phosphate can be assigned to the (b) isomer. These methods are dependent on the variations in physical constants which take place as the distance between charged groups of a zwitterion increases.[19]

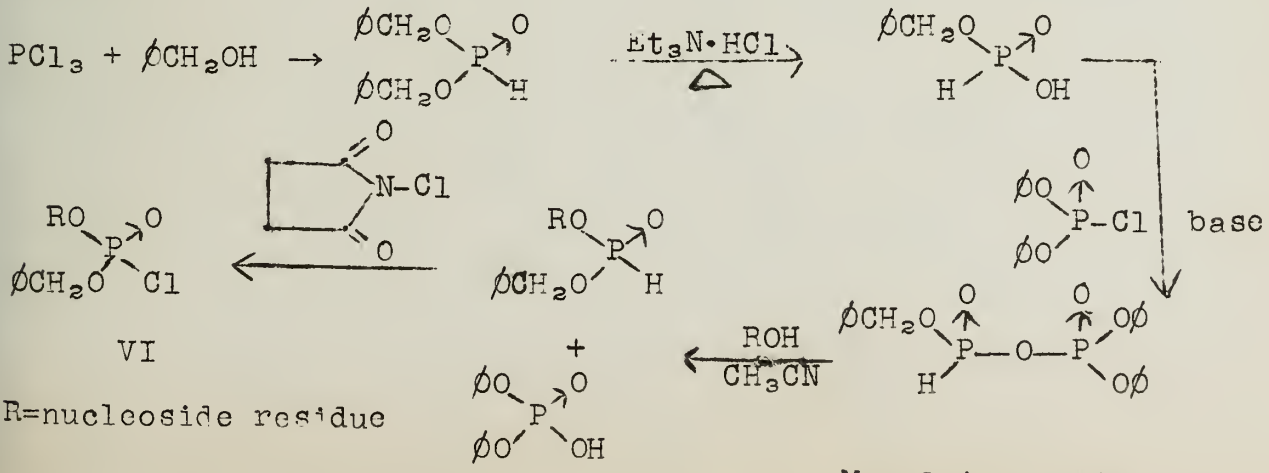
Polynucleotides

Todd has recently developed a synthetic route which should lead to a general method of synthesizing nucleotides.[17,20]

(VI)

R and R' are nucleoside residues.

Until very recently no nucleoside chlorophosphonates had been synthesized. A synthesis for nucleoside benzyl phosphites and a chlorination process were required. It was found that mixed phosphoric-phosphorous acid anhydrides would react with nucleosides to produce the phosphite esters. Chlorination with N-chloro-succinimide[4] led to the desired nucleoside benzyl chlorophosphonate (VI).

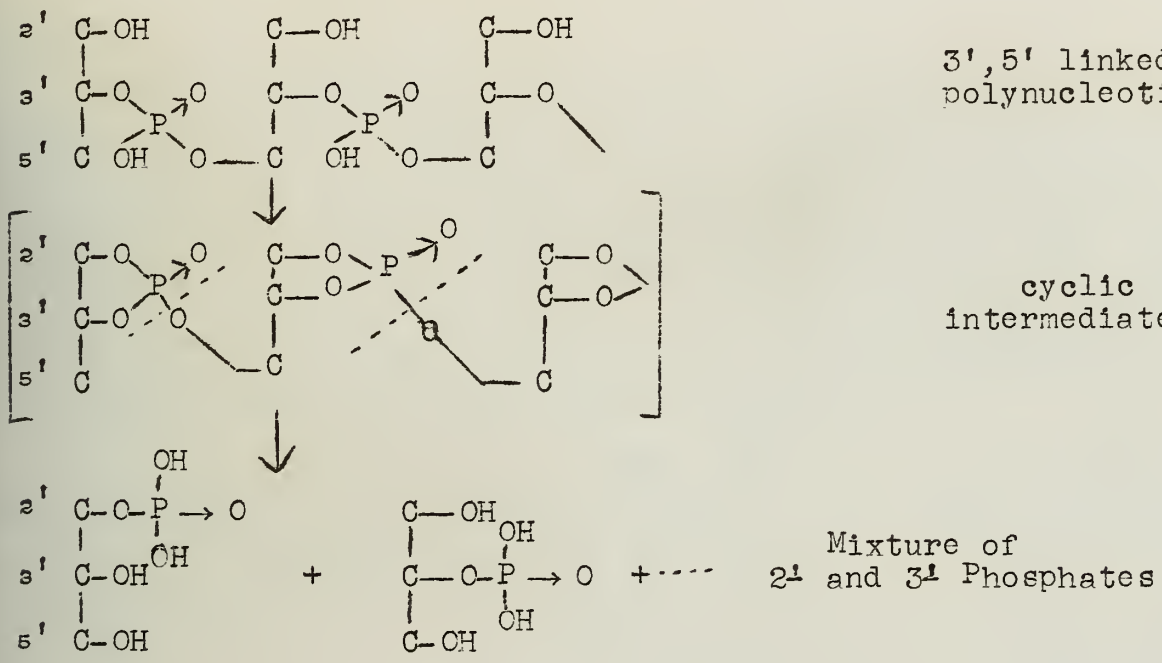


VI

R=nucleoside residue

Mixed Anhydride

Todd and coworkers have suggested a mechanism for the hydrolysis of nucleic acids which is based on a cyclic intermediate similar to that involved in the equilibriation of the (a) and (b) forms of adenylic acid.[21,22]



If rupture of only one bond attached to phosphorus in the intermediate is assumed, it can be seen that the rupture of either the 2' or 3' C-O-P bond would lead only to starting material or an isomer. Depolymerization would take place only by breakage of the 5' bond.

BIBLIOGRAPHY

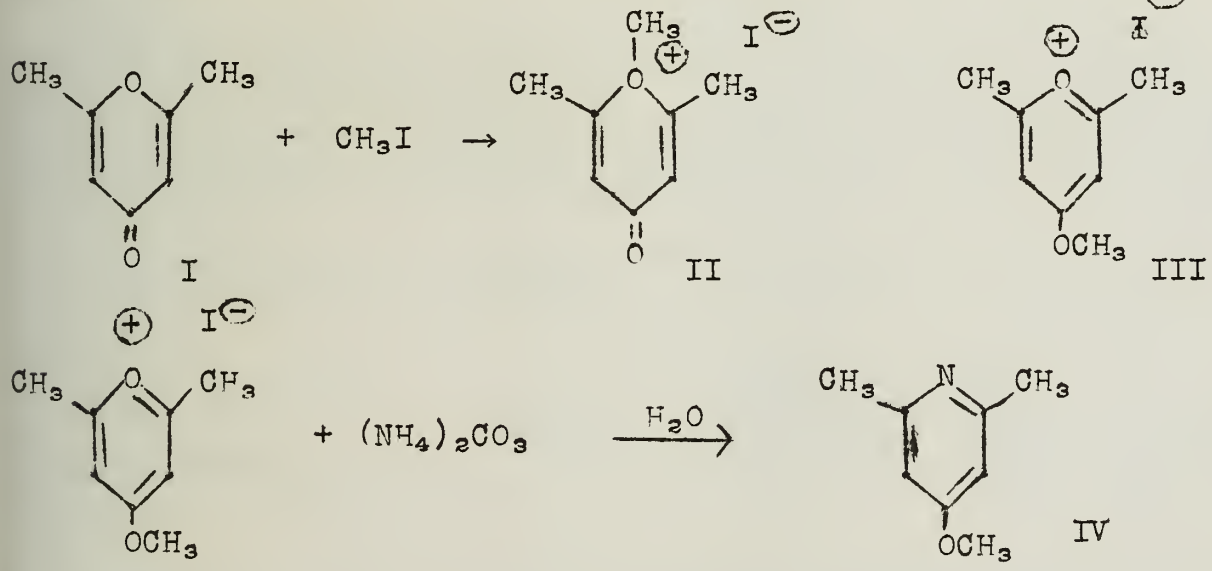
1. Atherton, Quart. Revs. London, 3, 146 (1949).
2. Atherton, Openshaw, and Todd, J. Chem. Soc., 382 (1945).
3. Todd, ibid., 647 (1946).
4. Kenner, Todd, and Weymouth, ibid., 3675 (1952).
5. Baddiley, Clark, Michalski, and Todd, ibid., 815 (1949).
6. Clark and Todd, ibid., 2030 (1950).
7. Brown, Haynes, and Todd, ibid., 3299 (1950).
8. Lythgoe and Todd, ibid., 592 (1944).
9. Baddiley and Todd, ibid., 648 (1947).
10. Baddiley, Michelson, and Todd, ibid., 582 (1949).
11. Michelson and Todd, ibid., 2487 (1949).
12. Levene and Tipson, J. Biol. Chem. 121, 131 (1937).
13. Michelson and Todd, J. Chem. Soc., 2476 (1949).
14. Gulland and Overend, ibid., 1380 (1948).
15. Haworth and Hirst, Ann. Rev. Biochem. 5, 82 (1936).
16. Carter and Cohn, Fed. Proc. 8, 190 (1949).
17. Corby, Kenner, and Todd, J. Chem. Soc., 1234 (1952).
18. Brown, Magrath, and Todd, ibid., 2708 (1952).
19. Cavalieri, J. Am. Chem. Soc., 74, 5804 (1952).
20. Corby, Kenner, and Todd, J. Chem. Soc., 3669 (1952).
21. Brown and Todd, ibid., 52 (1952).
22. Elmore and Todd, ibid., 3681 (1952).

TRIALKYL OXONIUM SALTS

Reported by Robert J. Lokken January 16, 1953

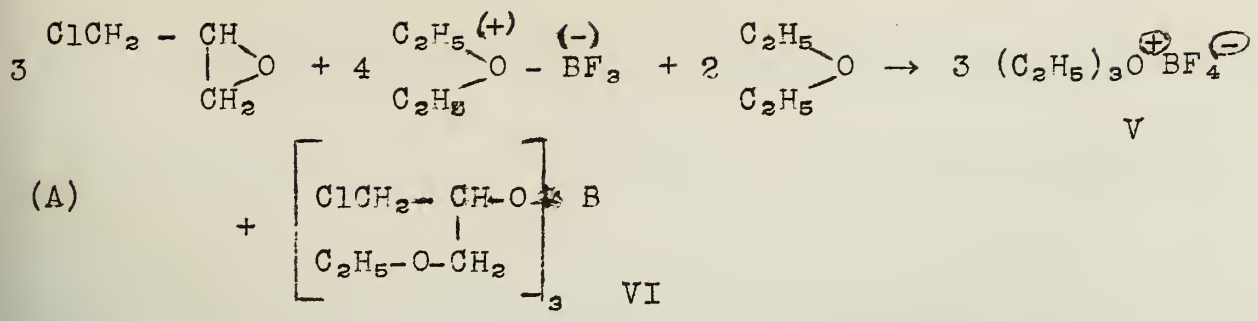
Synthesis

Trialkyl oxonium salts of the type $R_3O^+X^-$ such as (II) are such strong alkylating agents that all attempts to prepare them by the alkylation of ethers with alkyl halides or dialkyl sulfates have failed. In the alkylation of the cyclic ether, 2,6-dimethylpyrone (I), with methyl iodide a compound was obtained which was thought to be a trialkyl oxonium salt with structure (II). However, Baeyer showed that it was not a true trialkyl oxonium salt and that its structure was (III).[1] On treating the salt with aqueous ammonium carbonate solution he obtained 4-methoxylutidine (IV). This showed that the methyl group was not attached to the ring oxygen atom, but to the carbonyl oxygen.

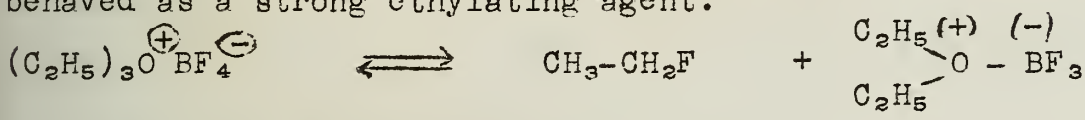


In 1937 Meerwein discovered a method for synthesizing trialkyl oxonium salts while studying the reaction of boron trifluoride etherates with epoxides.[5] Earlier he and Pannwitz had shown that alcohol-boron trifluoride complexes are strongly acidic. Since ethers can be considered to be alcohol anhydrides it was thought that the reactions of boron trifluoride etherates should be analogous to those of acid anhydrides. Then just as anhydrides react with epoxides to form esters of the corresponding glycols, boron trifluoride etherates would be expected to produce diethers.

When epichlorohydrin was added to an ether solution of boron trifluoride two products were formed. One was an ether-insoluble crystalline solid which was assigned structure (V). The other, an ether-soluble solid, was shown to be (VI).

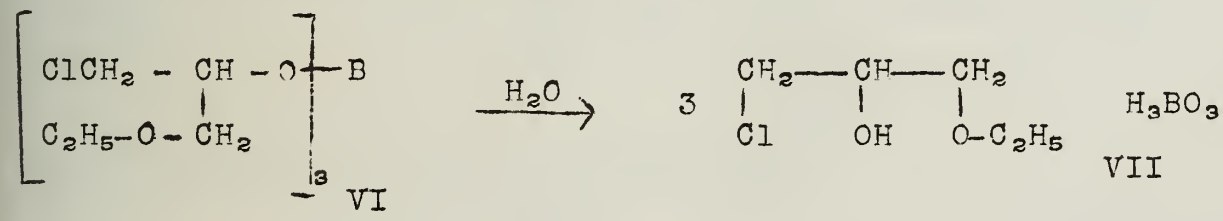


The structure of (V) was assigned on the basis of its carbon-hydrogen analysis, salt-like properties, and chemical behavior. It decomposed on heating to 100° to give ether and ethyl fluoride, and behaved as a strong ethylating agent.



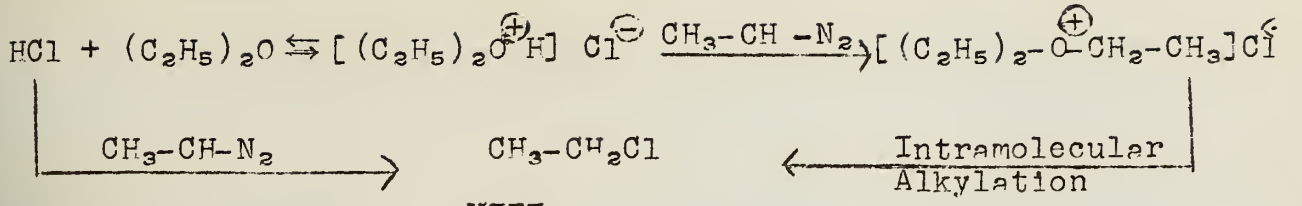
Meerwein found that the decomposition of the salt was reversible and prepared triethyl oxonium fluoroborate by letting boron trifluoride etherate, ethyl fluoride, and ether stand in a sealed tube at room temperature for three to four weeks. He also prepared dimethylethyloxonium fluoroborate from boron trifluoride dimethyl etherate and ethyl fluoride.

The assignment of structure (VI) was based on its analysis and on its hydrolysis to (VII).



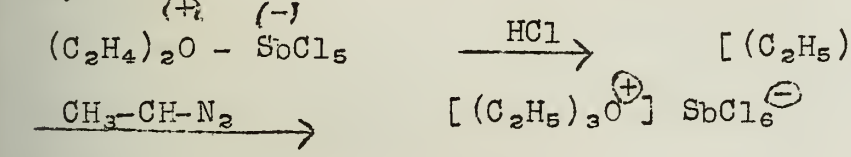
Recently a new synthesis of trialkyl oxonium salts was attempted by Klages and Meuresch in Germany.[4] Meerwein had used the strong formation tendency of the fluoroborate ion to overcome the resistance of ethers to alkylation. Klages and Meuresch thought that direct alkylation might be accomplished by a reaction the mechanism of which was different from that of the conventional type of alkylation. It was their theory that aliphatic diazo compounds should be capable of alkylating any compound which was sufficiently acidic. Accordingly, they tried to alkylate dialkyl oxonium salts (addition products of ethers and acids) with aliphatic diazo compounds.

Instead of the expected trialkyl oxonium halide, the alkyl halide (VIII) corresponding to the diazo compound was obtained. There are two possible paths to this alkyl halide as shown in the equation.



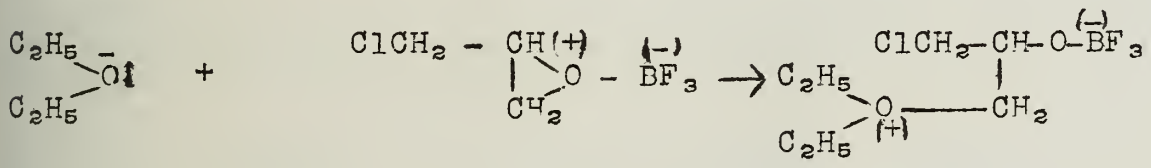
VIII

These results indicate that the dialkyl oxonium salt which is used must be one of a complex acid such as a hexachloroantimonate or a fluoroborate, since these etherates have practically no tendency to dissociate into ether and an acid, HX. In addition, these complex ions are much poorer nucleophilic agents than is chloride ion and will not attack the oxonium ion to give intramolecular alkylation.

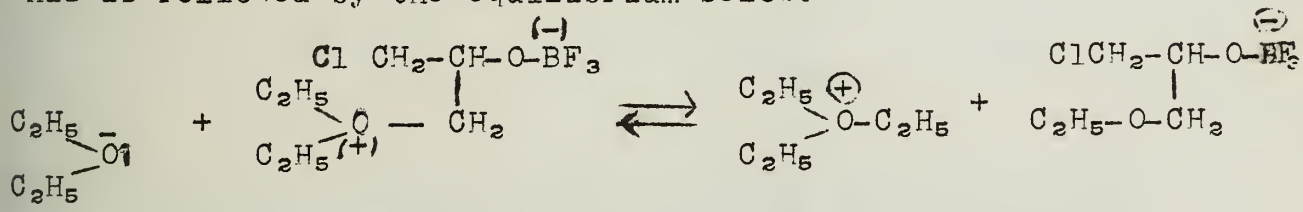


Mechanism

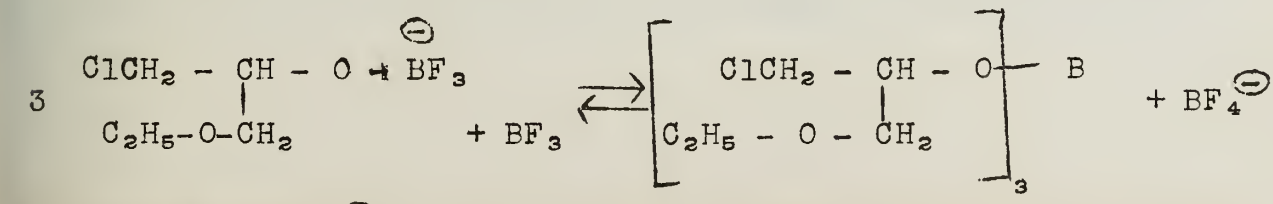
The mechanism of the reaction involved in Meerwein's synthesis has not been elucidated. The following scheme is proposed as a likely possibility. The key step is apparently the opening of the epoxide ring.



This is followed by the equilibrium below.

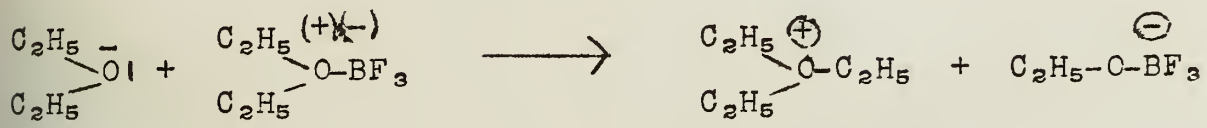


This equilibrium is driven to the right because of the excess of diethyl ether and because of the subsequent removal of the triethyloxonium ion as its insoluble fluoroborate. A further series of equilibrations redistributes the alkoxide and fluoride ions around boron.



The removal of $BF_4^{\ominus}$ as its insoluble triethyloxonium salt shifts this equilibrium to the right also.

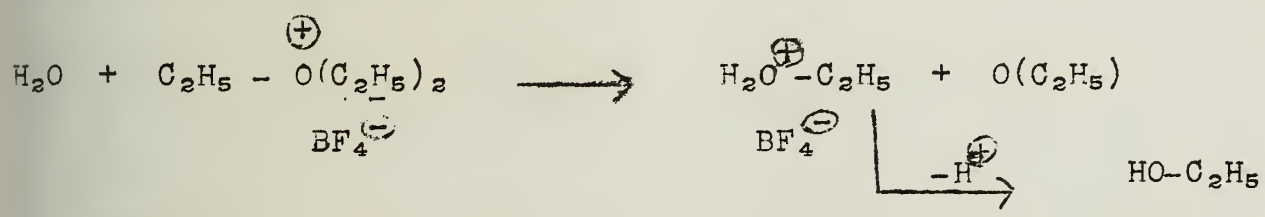
The reaction of diethyl ether with BF_3 shown below (which is known not to proceed) is formally analogous to that shown in equation (A).



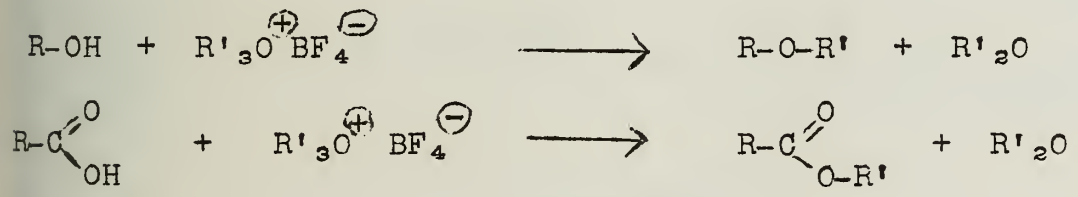
The success of the reaction in equation (A) is due to the driving force provided by the opening of the strained epoxide ring.

Chemical Reactions

Tertiary oxonium salts are the strongest alkylating agents known. That is to say, it is very easy for even a weakly nucleophilic agent to attack one of the alkyl groups replacing an ether molecule. They undergo a replacement reaction with water to form an ether and an alcohol.

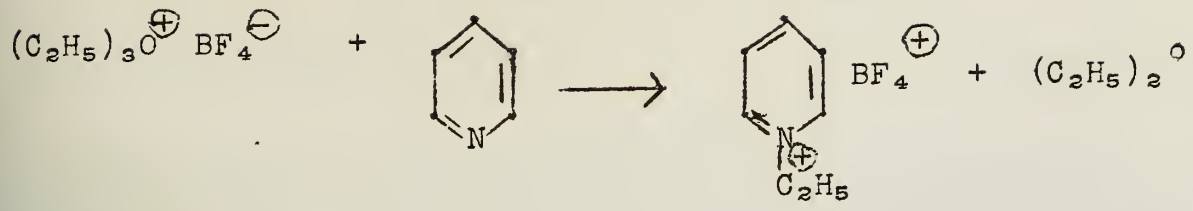


Alcohols, and even such weak bases as phenols, are readily alkylated by trialkyl oxonium salts to form ethers; and esters are formed from organic acids.

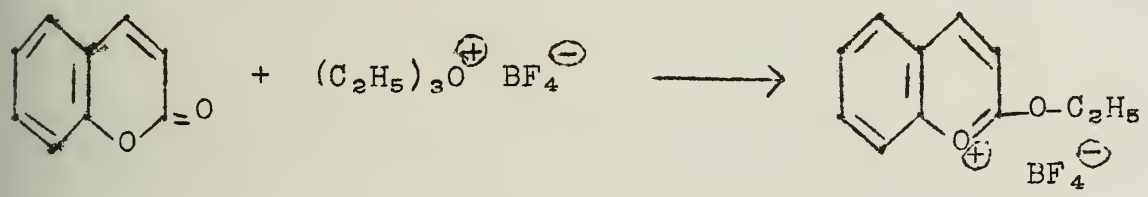


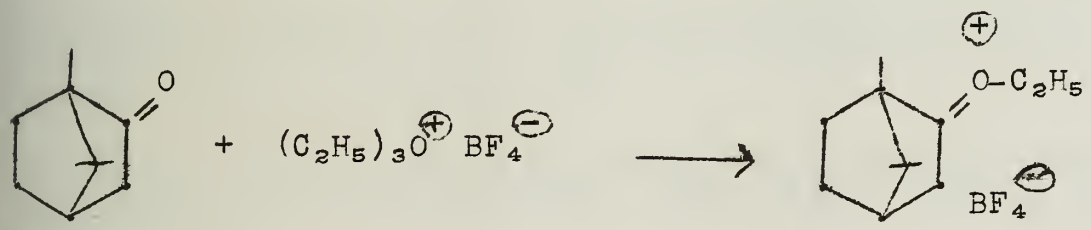
Alkali phenolates and alkali salts of acids are alkylated in aqueous alkaline solution even more readily than are the free phenols or acids.

Sulfur-, nitrogen-, or oxygen-containing bases are alkylated to form sulfonium, ammonium, or new oxonium salts. Thus pyridine is converted to ethyl pyridinium fluoroborate and diethyl sulfide to triethyl sulfonium fluoroborate in practically quantitative yield.



The tremendous alkylating power of the trialkyl oxonium salts is demonstrated by the fact that they can be used to alkylate coumarin and saturated and unsaturated ketones, while attempts to alkylate these compounds with the conventional alkylating agents have been unsuccessful.





BIBLIOGRAPHY

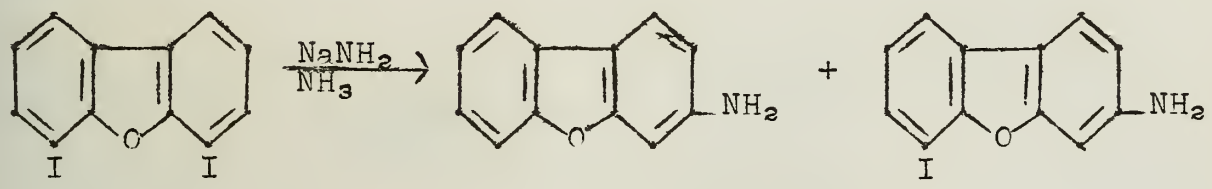
1. A. Baeyer, Ber., 43, 2337 (1910).
2. A. Baeyer and V. Villiger, Ber., 34, 2681 (1901).
3. Collie and Tickle, J. Chem. Soc., 75, 710 (1899).
4. Klages and Meuresch, Chem. Ber., 85, 863 (1952).
5. H. Meerwein and coworkers, J. prakt. Chem., 147, 257 (1937).

AMINATIONS WITH ALKALI AMIDES

Reported by Thomas R. Moore January 16, 1953

The reaction of monohalobenzenes with sodium amide or potassium amide in liquid ammonia to give anilines has been known for some time.[1] It has also been known that the monohalobenzenes when allowed to react with alkali dialkyl amides give N-substituted anilines[1] and that pyridine and quinoline react with alkali amides, placing an amino group on the carbon adjacent to the nitrogen in the ring.[2] But when Gilman and coworkers attempted to prepare 4,6-diaminodibenzofuran from the corresponding diiodo compound they came across the following apparently anomolous reaction.:[3]

I)



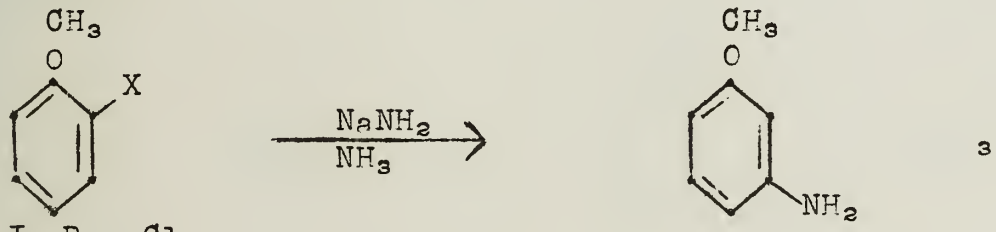
+ a diaminodibenzofuran

The diamino compound was proven not to be the 3,7 or 3,8, and was believed to be the 3,6.

It was then found that 4-iodo- or 4-bromodibenzofuran gave 3-aminodibenzofuran, while the 2-bromo compound gave the 2-aminodibenzofuran. It was soon found that 4-iododibenzothiophene showed a similar rearrangement.[4]

Other compounds were then studied in an attempt to determine the scope of this rearrangement. This study unearthed the following reactions:

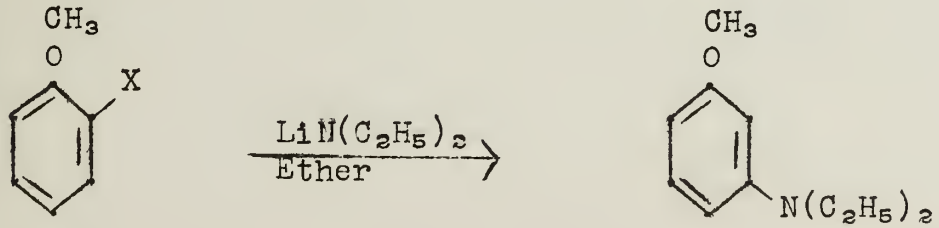
II)



3

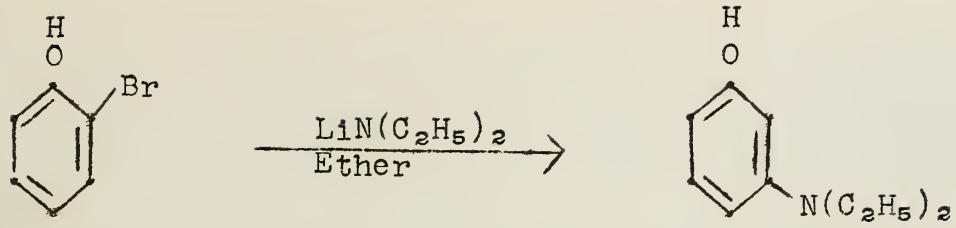
X = I, Br, Cl

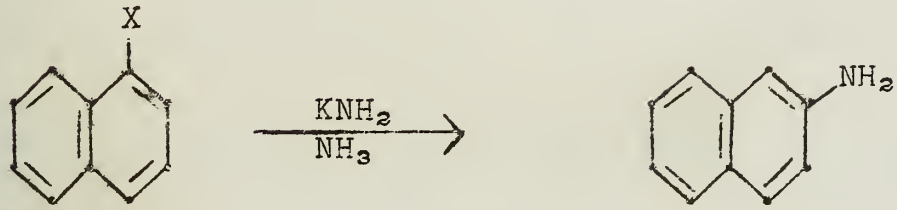
III)



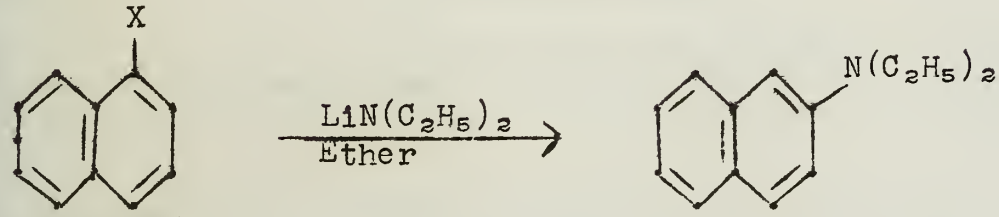
5

X = I, Br, Cl, F

IV) 

V) 

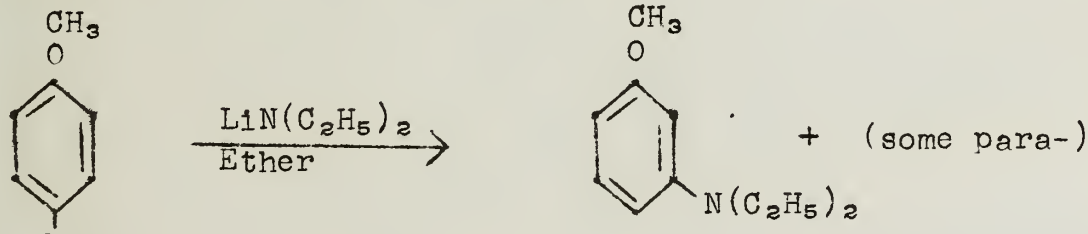
X = I, Br, Cl

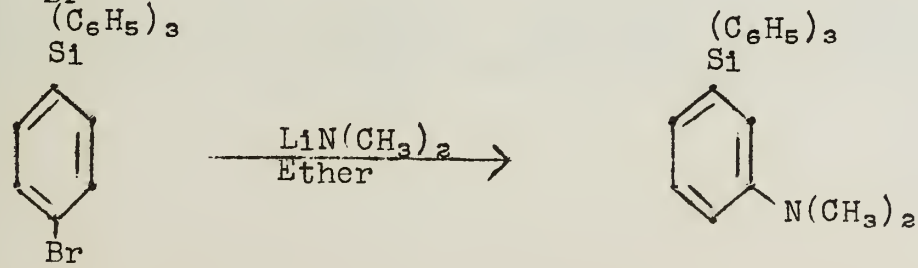
VI) 

X = I, Br, Cl, F

In reaction V it was noticed that α-fluoronaphthalene gave unrearranged product, unlike the other halogens. In reaction VI fluorine behaved as the other halogens did. It was also found that the β-halonaphthalenes gave β-naphthylamine with only small traces of α product.[7] α-Haloquinolines show no rearrangement.[8]

The same rearrangement was found to take place when the halogen is ortho to an N-substituted amino group[9] or a trifluoromethyl group.[10] That rearrangement from the para as well as from the ortho position occurs was proven by the following experiments.:[11,12]

VII) 

VIII) 

The order of reactivity of halogens in such reactions appears to be Br > I > Cl.[13] Gilman and co-workers have found that many alkali diamides will react, lithium di-n-butyl amide giving better yields than lithium diethyl amide. Lithium piperidide and morpholide have also been used.[6]

Benkeser and Buting[14] have attempted to discover the mode of formation of the products by a study of bromoanisoles containing a third substituent on the ring. Their conclusions are as follows:

1) The fact that 3-methyl-2-bromoanisole gives no product with sodium amide shows that the amino group goes to the position ortho to that of the halogen, not para. This is confirmed by the fact that 6-methyl-2-bromoanisole gives a 30% yield of 1-methyl-4-aminoanisole but no 1-methyl-2-aminoanisole.

2) The fact that 4-trifluoromethyl-2-bromoanisole gives unrearranged product shows that the trifluoromethyl is stronger in orienting power than the methoxyl is in rearrangement-producing power.

3) The fact that 2-bromo-4-methylanisole gives over 50% yield of 3-amino-4-methylanisole shows that the entrance of the amino group is not hindered by the presence of an ortho methyl group.

REFERENCES

1. F. Bergstrom and W. Fernelius, Chem.Rev., 20, 437 (1937).
2. M. T. Leffler, Organic Reactions, Vol. I, 91 (1942).
3. H. Gilman and S. Avakian, J. Am. Chem. Soc., 67, 349 (1945).
4. H. Gilman and J. Nobis, ibid., 67, 1479 (1945).
5. H. Gilman et al., ibid., 69, 2106 (1945).
6. H. Gilman and R. Kyle, ibid., 74, 3027 (1952).
7. R. Urner and F. Bergstrom, ibid., 67, 2108 (1945).
8. N. Luthy, F. Bergstrom, H. Mosher, ibid., 71, 1109 (1949).
9. H. Gilman, R. Kyle, R. Benkeser, ibid., 68, 143 (1946).
10. R. Benkeser and R. Severson, ibid., 71, 3838 (1949).
11. H. Gilman and R. Kyle, ibid., 70, 3945 (1948).
12. H. Gilman and H. Melvin, ibid., 72, 995 (1950).
13. F. Bergstrom and C. Horning, J. Org. Chem., 38, 254 (1946).
14. R. Benkeser and W. Buting, J. Am. Chem. Soc., 74, 3011 (1952).
15. C. Horning and F. Bergstrom, ibid., 67, 2110 (1945).
16. J. Bunnett and R. Zahler, Chem. Rev., 49, 273 (1951).

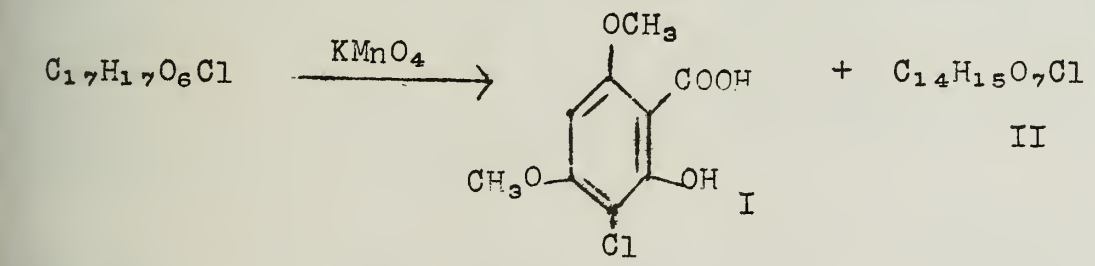
GRISEOFULVIN

Reported by P. D. Thomas January 16, 1953

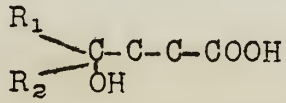
In 1938, Oxford and co-workers[1] isolated a metabolic product present in the mycelium of Penicillium Griseofulvum Dierckx which they named griseofulvin. It was found to be a colorless neutral compound, $C_{17}H_{17}O_6Cl$, m.p. 220°, [α] 5790 + 354°, containing three methoxyl groups. Subsequently, it was isolated from P. janczewskii [= P. nigricans] and its unique biological activity on moulds noted by Brian[2,3] and McGowan[4] who originally called it "curling factor" before the identity with griseofulvin was established.[5,6]

Oxford et al.[1] noted that griseofulvin gave no color with $FeCl_3$ and contained no free -OH or -COOH groups. The presence of a carbonyl group was established since a crystalline mono-oxime was readily obtained. They also noted that griseofulvin on acid hydrolysis afforded griseofulvic acid, $C_{16}H_{15}O_6Cl$, [α] 5461 + 50°, a monobasic acid containing two methoxyl groups and giving a feeble color with $FeCl_3$. Hydrolysis of griseofulvin or further hydrolysis of griseofulvic acid in 0.5 N NaOH yielded norgriseofulvic acid, $C_{15}H_{13}O_6Cl$, [α] 5461 + 609°, a dibasic acid containing only one methoxyl group, together with decarboxygriseofulvic acid $C_{15}H_{15}O_4Cl$, [α] 5461 - 31°, an insoluble neutral compound containing two methoxyl groups, giving no color with $FeCl_3$, and derived from griseofulvic acid by loss of one mole of CO_2. Decarboxygriseofulvic acid was found to be stable to acid hydrolysis, hence they concluded griseofulvin contained only one $-COOCH_3$ group and that the second acidic group in norgriseofulvic acid was a phenolic -OH group.

On oxidation of griseofulvin with $KMnO_4$ in acetone at room temperature two degradation products (I) and (II) were obtained.[1]



II, $C_{14}H_{15}O_7Cl$, [α] 5790 -24°, was a monobasic acid which gave no color with $FeCl_3$. It was shown to contain two $-OCH_3$ groups, a C=O group which cannot be a methyl ketone since it gave no iodoform with alkaline iodine, and a tertiary OH group. On treatment with acetic anhydride in pyridine it did not give an acetate but the elements of water were eliminated to give a neutral substance $C_{14}H_{13}O_6Cl$. The original substance, $C_{14}H_{15}O_7Cl$, is therefore probably a γ-OH acid of the form:

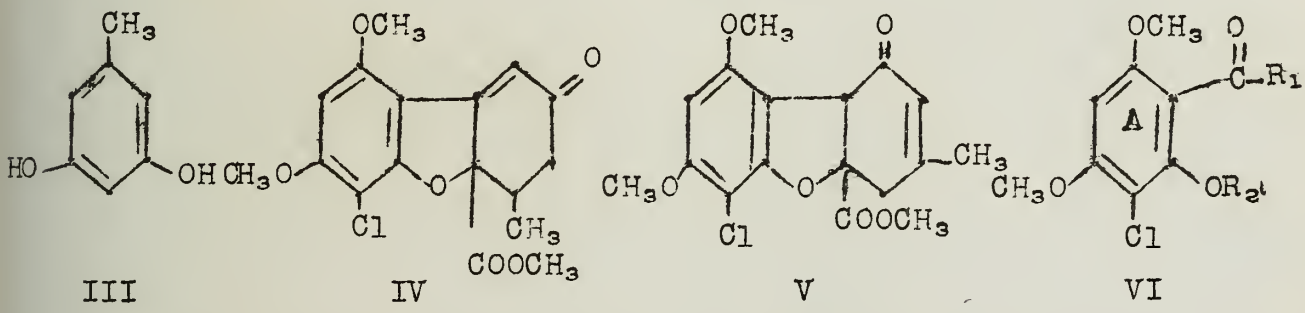


$R_1, R_2 \neq H$

Since II on further oxidation gave I, the structure XI-a was assigned to II.

Griseofulvin, on KOH fusion gave orcinol (III) which was concluded to be formed from a different part of the molecule than I.

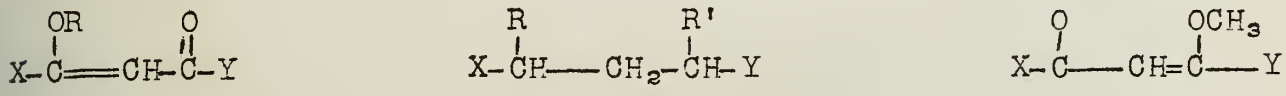
Oxford and co-workers[1] suggested the tentative structure IV which explained many of the experimental facts. This structure was at first supported, with slight modification (V), by Grove and McGowan[5] but it was later[7] rejected by them as incompatible with the ultraviolet and infrared absorption spectra of griseofulvin and its derivatives; they[7] concluded from the available spectroscopic and chemical evidence that: (a) griseofulvin contained the partial structure VI and (b) $-COOCH_3$ and $-COOH$ groupings were absent in griseofulvin and griseofulvic acid respectively, and the acidity of the latter compound was attributed to the enolic grouping VII-a.



Very recently Grove, MacMillan, Mulholland and Rogers[8-14] collaborated to revise the structure of griseofulvin and its derivatives. They repeated the work of Oxford[1] and agreed with the major portion of it. However, further work was required before the structure could be definitely established. The ultraviolet absorption of griseofulvin showed that the α,β-unsaturated ketone system postulated by Oxford et al.[1] could not be conjugated with the aromatic nucleus in griseofulvin as in IV. Neither did the absorption of griseofulvin agree particularly well with that predicted for V. Rather, in agreement with partial Structure VI, it was typical of a compound in which phloroglucinol and carbonyl chromophores were conjugated.[16,17]

These workers provided further chemical evidence for the inadequacy of formulas IV and V. Thus, while griseofulvin on mild hydrolysis with aquous alcoholic alkali gives griseofulvic acid, one of the reduction products, tetrahydrodeoxygriseofulvin, is very resistant to hydrolysis and this stability could not be dismissed on grounds of steric hindrance.[1,9,14] Further the fact that on slightly more vigorous hydrolysis with aqueous alkali griseofulvic acid gives as one of the products decarboxygriseofulvic acid, cannot be taken as proving the presence of the carboxylic acid group. They also found that griseofulvic acid possessed marked stability toward acid hydrolysis and suggested that the CO_2 lost in alkaline hydrolysis is derived from a carboxyl group which appears as a result of a molecular rearrangement under alkaline conditions.[13]

The difference in behavior of griseofulvin and tetrahydrodeoxygriseofulvin towards hydrolysis caused Grove and McGowan[7] to suggest that griseofulvin contained the grouping VII-b, a methyl enol ether of a 1,3 diketone; griseofulvic acid, VII-a. In tetrahydrodeoxygriseofulvin this would become VIII-a in which the methoxyl group is attached to a saturated carbon atom and would then resist hydrolysis.



VII (a) R=H
(b) R=CH_3

VIII (a) R=OCH_3; R'=H
(b) R=R'=OH
(c) R=H; R'=OH
(d) R=R'=H

IX

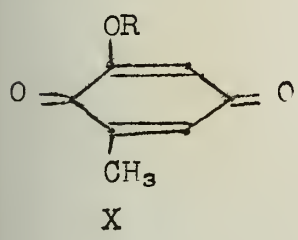
Oxford et al.[1] observed that an isomer, m.p. 200-201°, $[\alpha]^{19}$ 5790 + 223°, of griseofulvin was formed mixed with an approximatel equal amount of griseofulvin, when griseofulvic acid or norgriseofulvic acid was methylated with diazomethane. It appeared likely on the above hypothesis that isogriseofulvin would prove to be the isomeric methyl ether (IX), although no evidence was offered at that time. Grove et al.[9] in their most recent work have shown that isogriseofulvin can be easily made and in good yield by the action of methanolichydrochloric acid on griseofulvin. Isogriseofulvin is easily hydrolysed by dilute aqueous-alcoholic alkali to griseofulvic acid, which has the same optical rotation and configuration as that prepared from griseofulvin; the isomerism is thus not connected with asymmetry around a particular carbon atom, but arises from the presence of a tautomeric system (XII) in griseofulvic acid. Isogriseofulvin also differs from griseofulvin in that it does not readily form derivates with ketonic reagents.[9]

Reduction of griseofulvic acid[13] provided further evidence against the presence of a carboxylic acid group. When Adam's platinum oxide catalyst in acetic acid was used, two neutral non-lactonic alcohols, $C_{16}H_{19}O_6Cl$ (A) and $C_{16}H_{19}O_5Cl$ (B) were isolated together with small amounts of a neutral non-lactonic compound, $C_{16}H_{19}O_4Cl$ (C). If the acidic component of griseofulvic acid is VII-a, these compounds can be written with the partial structures VIII-b, VIII-c and VIII-d respectively. The reduction product B was oxidized by chromic acid to the corresponding ketone, $C_{16}H_{17}O_5Cl$, indicating that the -OH is secondary. The ultraviolet absorption curve of A shows that the main chromophoric system, VI, of griseofulvin is unaffected by reduction and since the chemically unreactive carbonyl group of griseofulvin can be identified in A by its infrared spectrum (band at 1685 cm^{-1}) it follows that this carbonyl group must be the one in the partial structure VI. This unreactive carbonyl group can also be identified in the spectra of reduction products B (band at 1682 cm^{-1}) and C (band at 1695 cm^{-1}); A and B show typical alcoholic -OH absorption (at 3401 and 3425 cm^{-1} respectively), which is absent in the spectrum of C.

From oxidative degradation[10,11] it was concluded that griseofulvin possesses a benzenoid ring (A) and a hydroaromatic six-membered ring (C) thereby confirming the views of Oxford et al.[1].

The nature and orientation of ring A follows from the formation of 3-chloro-2-hydroxy-4, 6-dimethoxybenzoic acid (I) from griseofulvin by oxidation with zinc permanganate in acetone -- conditions which are considered to preclude rearrangement. The structure of I has been established by two unambiguous syntheses.[11]

The presence of a second six-membered ring (C) in griseofulvin is indicated by oxidation with chromic oxide to 3-methoxy-2, 5-toluquinone (X; R = CH_3) and by formation of orcinol (III) by KOH fusion. Since the three methoxyl groups in griseofulvin appear in the oxidation products (I and X; R = CH_3) it is evident that the griseofulvin is not the methyl ester of a carboxylic acid.



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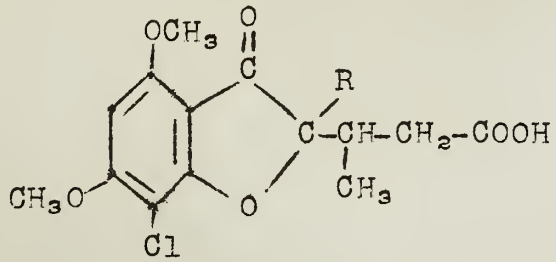
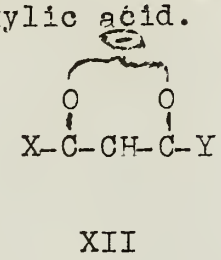


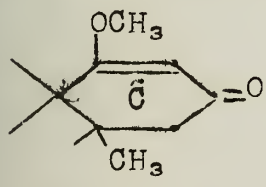
XI (a) R=OH
(b) R=H



XII

All the carbon atoms in griseofulvin are accounted for in the oxidation products (I) and (X; R = CH_3). That none of them is common to both rings A and C has been demonstrated by cleavage of griseofulvin,[12] in significant yield, into the acid I and orcinol monomethyl ether by 2 N sodium ethoxide. A similary fission[14] has been encountered in the alkaline hydrolysis of dihydrogriseofulvin which yields the salicylic acid (I) (derived from ring A) and m-cresol (from ring C). Moreover, formation of (I) under hydrolytic conditions[12] provides convincing chemical proof that there is a carbonyl group directly attached to the benzenoid ring (A) as suggested by spectroscopic evidence.

The hydroaromatic ring (C) must contain the C-methyl group and the olefinic double bond known to be present in griseofulvin. Moreover, if it is assumed that rearrangement does not occur in the formation of orcinol (III) and its monomethyl ether two potential hydroxyl groups must be located in the 3,5 positions with respect to the C-methyl group. Finally, ring C must contain the methyl ether group of the system VII-b; the most likely skeleton of ring C therefore appears to be XIII.



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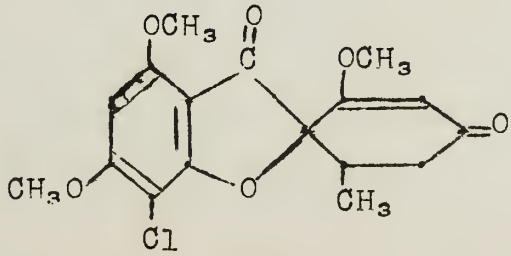

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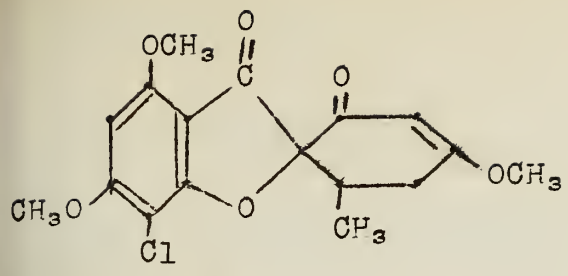
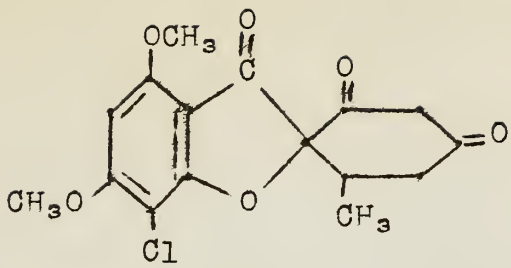


XV



XVI

The manner in which the two partial structures VI and XIII are linked in griseofulvin, the authors propose, is unequivocably determined by the formation of the acids $C_{14}H_{15}O_6Cl$ and $C_{14}H_{15}O_7Cl$ which were shown to be XI-b and XI-a respectively. Final proof comes from the oxidation with periodic acid, in which 1 mol. of periodate is consumed and the acid XI-a is split quantitatively into I and (+) methylsuccinic acid, identical with an authentic specimen. These acids, derived from griseofulvic acid by alkaline peroxide and by permanganate oxidation respectively, are substituted coumaran-3-ones in which the carbonyl and oxygen ether bridges from partial structure VI are linked to the same carbon atom, adjacent to a C-methyl group. Union of partial structures VI and XIII in a like manner leads to the two spiran structures XIV and XV which are isomeric methyl ethers of the tautomeric enol XVI and are therefore considered to represent griseofulvin and isogriseofulvin although not necessarily respectively. It is considered that XIV is more likely to give rise to 3-methoxy-2,5-toluquinone (X; R = CH_3) on chromic oxide oxidation and therefore represents griseofulvin. Isogriseofulvin, on the other hand, does not yield a quinone with CrO_3 and is therefore considered to be XV: the o-quinone which this structure might be expected to yield has not been isolated; it probably does not survive the oxidation.[12]

BIBLIOGRAPHY

1. A. E. Oxford, H. Raistrick and P. Simonart, Biochem. J., 33, 240 (1939).
2. P. W. Brian, P. J. Curtis and H. G. Hemming, Trans. Brit. Mycol. Soc., 29, 173 (1946).
3. P. W. Brian, Ann. Bot., 13, 59 (1949).
4. J. C. McGowan, Trans. Brit. Mycol. Soc., 29, 188 (1946).
5. J. F. Grove and J. C. McGowan, Nature, 160, 574 (1947).
6. P. W. Brian, P. J. Curtis and H. G. Hemming, Trans. Brit. Mycol. Soc., 32, 30 (1949).
7. J. F. Grove and J. C. McGowan, Chem. and Ind. 647 (1949).
8. J. F. Grove, D. Ismay, J. MacMillan, T. P. C. Mulholland and M. A. T. Rogers, Chem. and Ind. 219 (1951).
9. J. F. Grove, J. MacMillan, T. P. C. Mulholland, and M. A. T. Rogers, J. Chem. Soc., 3949 (1952).
10. J. F. Grove, D. Ismay, J. MacMillan, T. P. C. Mulholland and M. A. T. Rogers, ibid., 3958 (1952).
11. J. F. Grove, J. MacMillan, T. P. C. Mulholland and J. Zealley, ibid., 3967 (1952).
12. J. F. Grove, J. MacMillan, T. P. C. Mulholland and M. A. T. Rogers, ibid., 3977 (1952).
13. T. P. C. Mulholland, ibid., 3987 (1952).
14. T. P. C. Mulholland, ibid., 3994 (1952).
15. P. Haas, ibid., 89, 187 (1906).
16. G. Lindstedt, Acta Chem. Scand. 4, 772 (1950).
17. R. A. Morton and Z. Sawires, J. Chem. Soc. 1052 (1940).

STRAINED HOMOMORPHS

Reported by Seymour Pomerantz February 13, 1953

In 1942 Brown, Schlesinger, and Cardon[11] first proposed that the study of molecular addition compounds should furnish a convenient tool for the estimation of steric strains in related carbon compounds. It was believed that steric effects in ethane derivatives, for example, should reveal themselves in other ways than by restricted rotation. The repulsion of the two parts of the molecule should result in a weakening of the bond joining them. Measurement of this weakness in simple hydrocarbons cannot generally be effected, but a study of compounds with similar molecular dimensions (called homomorphs) can lead to an estimation of this strain.

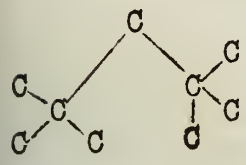
The geometry of the boron-nitrogen bond is almost identical with that of the carbon-carbon bond. The bond distances[11] are 1.54 Å for carbon-to-carbon and 1.58 Å for boron-to-nitrogen. Strains should be duplicated, but the effect of such strains should be considerably magnified by the comparative weakness of the donor-acceptor bond.

Spitzer and Pitzer[14] have discussed this relationship between strains in addition compounds and strains in hydrocarbons. It is apparent, however, that the concept need not be restricted to hydrocarbons. Replacement of one or more atoms or groups in the hydrocarbon by other atoms or groups of closely similar dimensions should result in the formation of molecules with widely different functional groups, but with closely related strains.

Examples of five series of homomorphs are given on page two (2).

Homomorphs of Di-t-butylmethane. Examples of these are shown in Fig. 1. An estimate of the strain is provided by comparing the heats of dissociation for t-butylamine-trimethylboron (13.0 kcal.)[4], and for the corresponding n-butylamine derivative (18.4 kcal.). The difference (5.4 kcal.) is attributed to steric strain in the t-butylamine-trimethylboron. It follows from the proposed thesis that a steric strain of this magnitude should be present in homomorphs of di-t-butylmethane. The thesis is supported by the value of the steric strain in di-t-butylmethane, estimated from heats of combusion to be 5.2 kcal. Other confirmatory evidence is found in the difficulty in preparing di-t-butylether (IX), the ease of solvolysis of neopentyldimethylcarbinylchloride (VIII)[1,5,7], the slow rate of reaction of neopentyldimethylamine with methyl iodide to form VII[6], and the instability of the addion compound of neopentyldimethylamine with trimethylboron[9].

Homomorphs of
di-t-butylmethane



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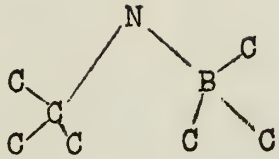

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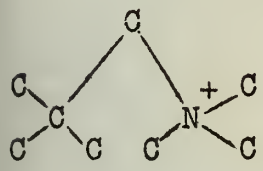

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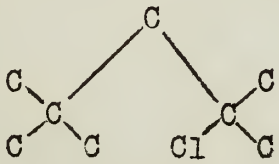

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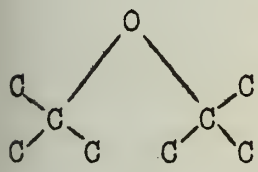

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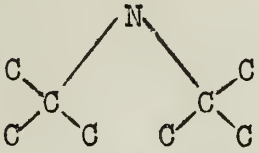
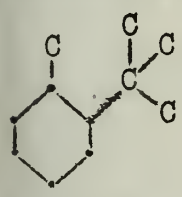


X

Fig. 1

Homomorphs of o-t-butyltoluene



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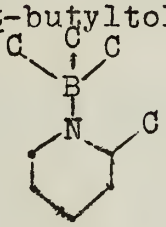

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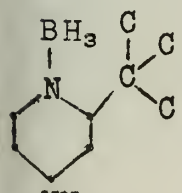

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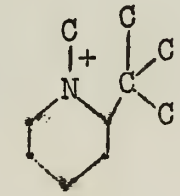

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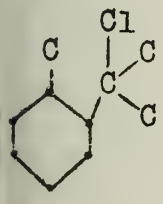

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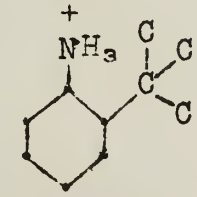
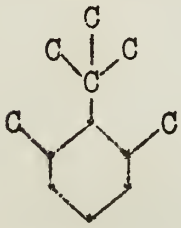


XXIII

Fig. 5

Homomorphs of 2,6-dimethyl-
t-butylbenzene



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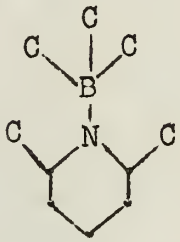

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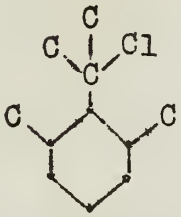

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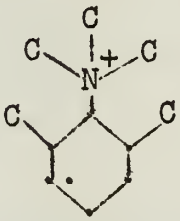
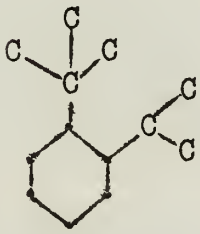


XIII

Fig. 2

Homomorphs of o-di-t-butyl-
benzene



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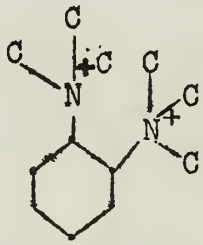
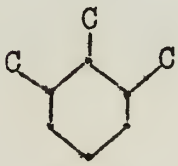


XVII

Fig. 3

Homomorphs of hemimellitene



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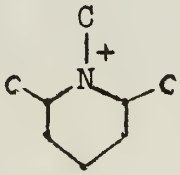

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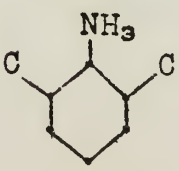

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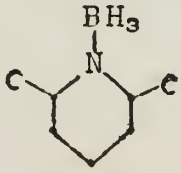


XXVII

Fig. 4

Homomorphs of 2,6-Dimethyl-t-butylbenzene. Trimethylboron forms a stable compound with pryidine, with a heat of dissociation of 17.0 kcal.[3]; but with 2,6-lutidine, a stronger base inaqueous solution, trimethylboron does not react to form XII. This points to a strain of at least 17 kcal. in these homomorphs. The parent hydrocarbon (XI) is not known and could not be prepared.[8] Over a period of several months no significant reaction of 2,6,N,N-tetramethylaniline to form XIII was observed[8]. 2,6-Di-methylphenylcarbinol and mesityldimethylcarbinol were prepared, but they could not be converted to the corresponding chlorides[8].

Homomorphs of o-Di-t-butylbenzene . The heat of reaction of boron trifluoride with pyridine (and with trimethylamine) is about 25 kcal, but boron trifluoride fails to add to o-t-butyl-N, N-dimethylaniline. This points to a strain of about 25 kcal. in this series of homomorphs[9]. It follows that such homomorphs should be exceedingly difficult if not impossible to prepare.

Homomorphs of Hemimellitene (1,2,6-trimethylbenzene). From the heats of combustion of the trimethylbenzenes[13], hemimellitene (XXIV) appears to be about 1.2 kcal. less stable than its isomers. The energies of activation of the reactions of pyridine and 2,6-lutidine with methyl iodide (XXV) are 13.9 and 14.9 kcal/mole, respectively. It may be significant that the 1.0 kcal. difference in energy of activation is in fair agreement with the strain predicted from combustion data. m-2-Xylidinium ion (XXVI) is the conjugate acid of m-2-xylidine, which has a pK_a of 3.42 vs. 4.25 for aniline. But the operation of both the inductive effect and steric inhibition of resonance should tend to increase the strength of m-2-xylidine.

Homomorphs of o-t-Butyltoluene. From the observation that the heats of reaction of boron trifluoride with pyridine and 2-t-butylpyridine are 25.0 and 14.8 kcal., respectively, an upper limit to the strain of 10 kcal. can be placed. But since the steric requirements of the borine group (BH_3) are considerably smaller than for boron trifluoride, the actual strain must be considerably lower. The energies of activation for the reaction methyl iodide with pyridine and 2-t-butylpyridine (XX) in nitrobenzene solution are 13.9 and 17.5 kcal., respectively. The value of 3.6 kcal., then, can be tentatively adopted as a lower limit to the strain.

SUMMARY

Model Homomorph	Strain Energy (kcal./mole)
Hemimellitene	1-2
o-t-Butyltoluene	4-6
Di-t-butylmethane	5.4
2,6-Dimethyl-t-butylbenzene	$\geqslant$ 17
o-Di-t-butylbenzene	$\geqslant$ 25

REFERENCES

1. H. C. Brown, Science, 103, 385 (1946).
2. H. C. Brown, et.al., J. Am. Chem. Soc., 75,1 (1953).
3. H. C. Brown and G. K. Barbaras, ibid., 69, 1137 (1947).
4. H. C. Brown, ibid., 75, 6 (1953).
5. H. C. Brown and H. L. Berneis, ibid., 75 10(1953).
6. H. C. Brown and W. H. Bonner, ibid., 75, 14(1953).
7. H. C. Brown and R. S. Fletcher, ibid., 71, 1845 (1949).
8. H. C. Brown and M. Grayson, ibid., 75, 20 (1953).
9. H. C. Brown and R. B. Johannesen, ibid., 75, 16 (1953).
10. H. C. Brown and K. L. Nelson, ibid., 75, 24 (1953).
11. H. C. Brown, H. I. Schlesinger, and S. Z. Cardon, ibid., 64, 325 (1942).
12. D. P. Evans, H. B. Watson, and R. Williams, J. Chem. Soc., 1345, 1348 (1939).
13. W. H. Johnson, E. J. Prosen, and F. D. Rossini, J. Research Natl. Bureau of Standards, 35, 141 (1945).
14. R. Spitzer and K. S. Pitzer, J. Am. Chem. Soc., 70, 1261 (1948)

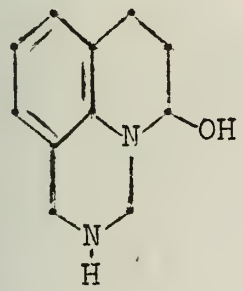
The Structure of Cytisine

Reported by Blaine O. Schoepfle February 13, 1953

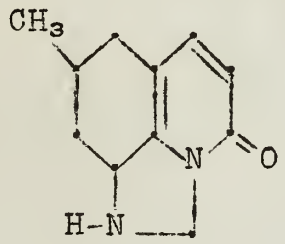
The alkaloid cytisine was first isolated in 1865[1], however, the correct emperical formula, $C_{11}H_{14}ON_2$, was not determined until 1890.[2]

A Zerevitinov determination indicated that the alkaloid contained one active hydrogen while the formation of a mono-N-acyl derivative fixed it as being attached to a nitrogen rather than to the oxygen.

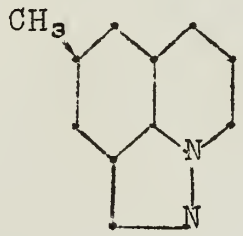
The reduction of cytisini with HI/P yielded several 6,8-dimethyl quinolines[3,4] and subsequently led to the structural proposals of Freund (I), Späth (II), and Ewins (III).



(I)



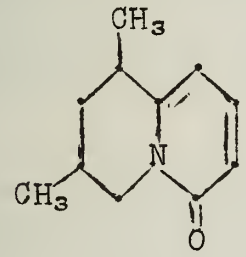
(II)



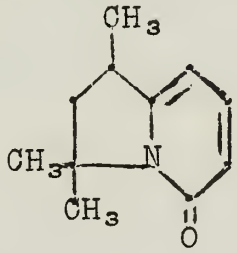
(III)

Structures (I) and (II) were eventually discarded[5] since they do not contain a potential 6,8-dimethyl quinoline nucleus and since the corresponding N-methyl quinolines were shown incapable of rearranging to the required 6,8-configuration.[6]

Ing soon questioned the presence of a quinoline nucleus in cytisine and theorized upon the rearrangement of (IV) and (V) type structures to quinolines under the influence of HI/P[4].

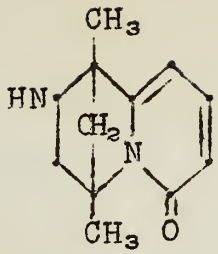


IV

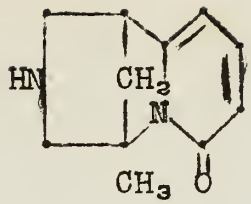


V

The first exhaustive methylation studies of cytisine yielded a dimer, $C_{22}H_{22}O_2N_2$[5]. This result implied the absence of H_β[7], a condition which is satisfied only by a formula of type (V), of which there are two, (VI) and (VII).

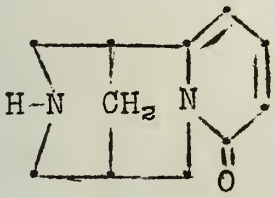


(VI)

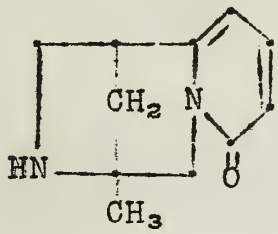


(VII)

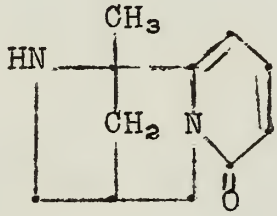
Subsequent exhaustive methylations have shown that the dimerization can be avoided[8], thus, structures (VI) and (VII) were rejected in favor of a type (IV) structure. Five structures (VIII - XII) of this type must be considered.



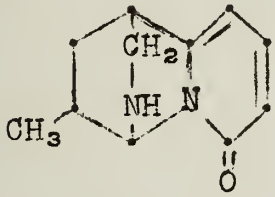
VIII



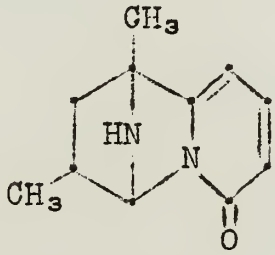
IX



X



XI



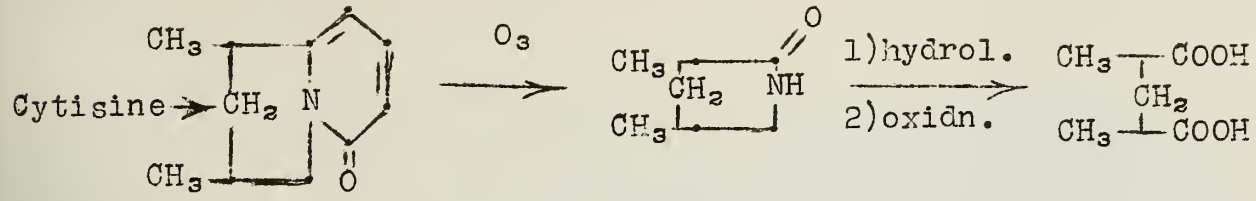
XII

The oxidation of N-methylcytisine yielded two isomeric compounds, $C_{12}H_{14}O_2N_2$[9]. These compounds were shown to be lactams in which the CH_2-N(CH_3)- group in methylcytisine had been oxidized to -CO-N(CH_3)-. Thus, structures (IX), (X), and (XII) can be eliminated since there is no chance of isolating isomers from the oxidation of there N-methylated derivatives.

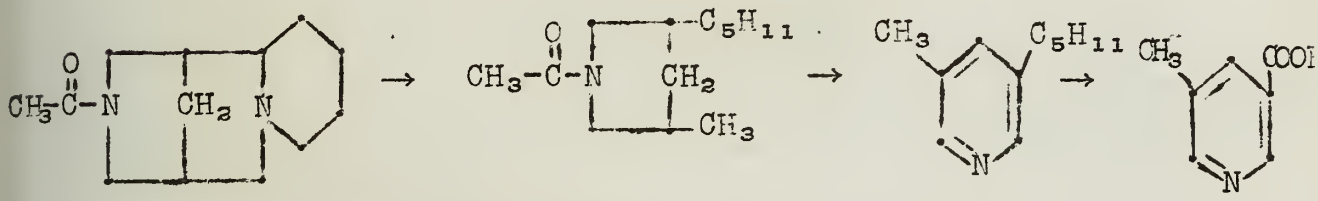
A choice between (VIII) and (XI) was made on the basis that N-benzenesulphonyl-N-methyl-β-cytisamic acid looses CO_2 at its melting point, whereas the α-acid derivative melts without decomposition.[9] One of the isomeric N-benzenesulphonyl derivatives of (VIII) would be expected to loose CO_2 in the same manner as demonstrated in the case of 6-hydroxy-4-methylpyridyl-2-acetic acid.[10] This difference between the α and β-derivatives would be difficult to explain in the case of structure (XI).

Subsequent proof for structure (VIII) has been demonstrated by:

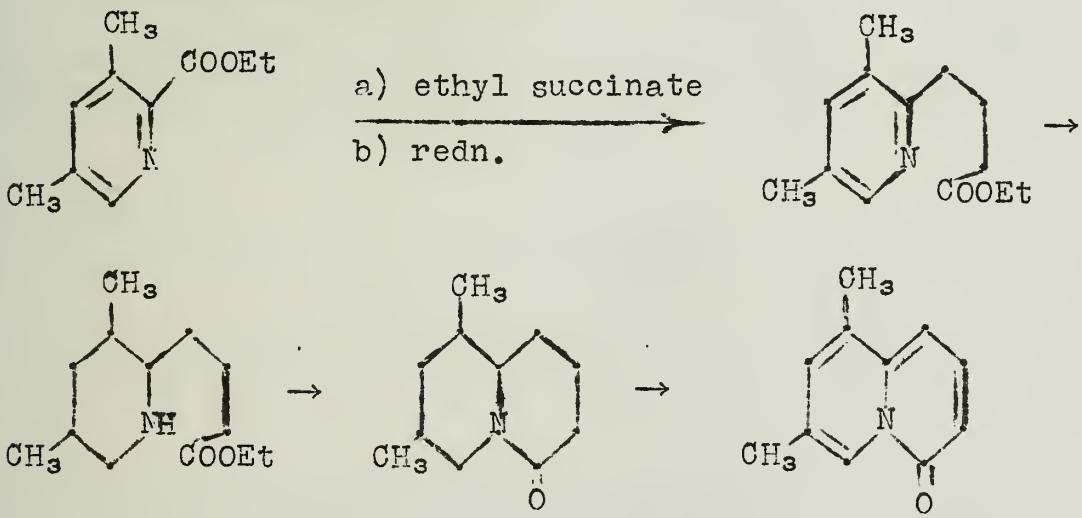
a) Ozonolysis of the exhaustive methylation product, hydrolysis, and oxidation to α,α'-dimethylglutaric acid.[8]



b) Exhaustive methylation of N-acetyl-tetrahydrodioxy-cytisine (XIII) and the subsequent conversion of its product to β-methylnicotenic acid[11].



c) The degradation of cytisine to (XIV)[12] and its subsequent synthetical conformation.[13]



XIV

Bibliography

1. Hausemann and Marme', Z. Chem., 1, 161 (1865).
2. Partheil, Ber. 23, 3201 (1890).
3. Ewins JCS 103, 97 (1913).
4. Späth, Monatsh. 40, 93 (1919).
5. Ing, JCS, 2195, (1931).
6. Späth, Monatsh. 40 15, 93 (1919).
7. Ingold and Jessop, JCS, 2357 (1929).
8. Späth and Galinovsky, Ber. 65, 1526 (1932).
9. Ing, JCS, 2778 (1932).
10. Collie JCS 71, 299 (1897).
11. Späth and Galinovsky, Ber. 66, 1338 (1933).
12. Indem, ibid., 69, 761 (1936).
13. Indem, ibid., 71, 721 (1938).

PHOTOCHEMICAL REACTIONS OF DIAZOMETHANE

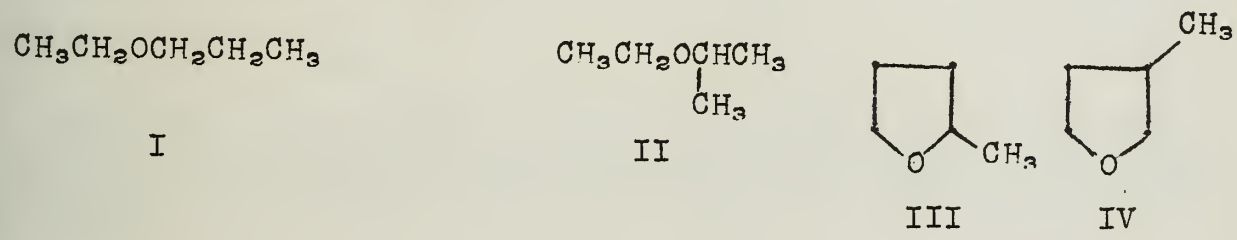
Reported by David B. Kellom February 20, 1953

Although diazomethane has been frequently employed as a methylating reagent for phenols and other compounds containg acidic hydroxyl groups, its light-catalyzed reactions with organic compounds have only recently attracted attention. Therefore, it is the purpose of this seminar to review some of the recent work on the photochemical reactions of diazomethane with a number of organic compounds.

Photochemical Reactions with Ethers

In 1901 Hantzsch and Lehman[1] reported that a solution of diazomethane in ether slowly lost its yellow color on exposure to light. This reaction gave according to Curtius[2] a viscous residue together with an evolution of gas, presumably nitrogen and ethylene However, it was not until forty years later that this reaction received further study.

From an examination of the evolved gases and the vaseline-like residue, Meerwein and co-workers[3] could account for only about 22% of the diazomethane that had been irradiated in diethyl ether. Careful fractionation of the solvent established the presence of ethyl n-propyl ether (I) and ethyl i-propyl ether (II). When tetrahydrofuran was used as the solvent, α- and β-methyltetrahydrofuran (III and IV) were isolated.



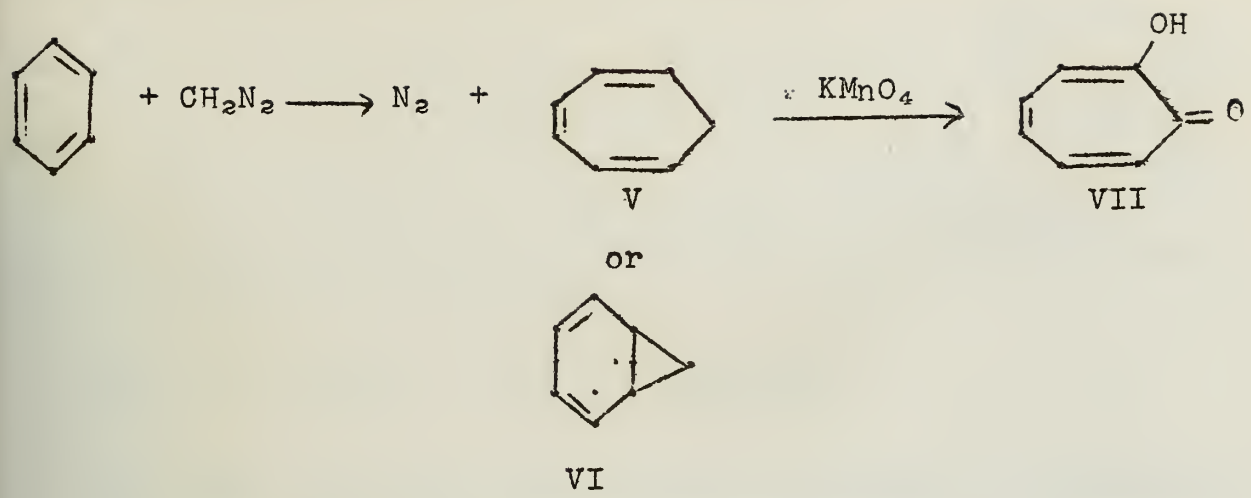
Similarly the photochemical decomposition of diazomethane in i-propyl aclohol gave products corresponding to the addition of a fragment CH_2 to the solvent. Indeed these results do suggest the presence of a highly reactive, high energy fragment.

$$CH_2N_2 \longrightarrow N_2 + :CH_2$$

Structures containing divalent carbon were frequently suggested by early chemists.[4-6] But only in the thermal or photochemical decompositions of diazomethane or ketene have such intermediates been definitely established.[7]

Photochemical Reactions with Hydrocarbons

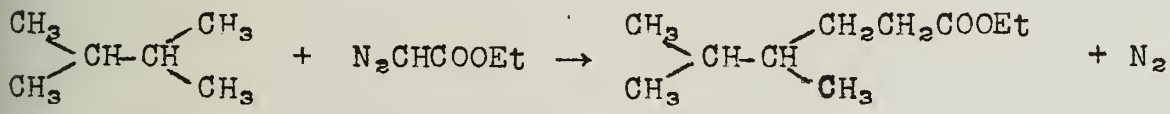
From the irradiation of a solution of diazomethane in benzene, Doering and Knox[8] reported the isolation of a small amount of a hydrocarbon, C_7H_8 (V or VI), identical with a sample of "cycloheptatriene" prepared by Kohler[9] from cycloheptanone. On oxidization with potassium permanganate the hydrocarbon gave tropolone (VII).



The structure of the hydrocarbon has not been definitely established. But it is interesting to note in this connection, the recent case of valence tautomerism Cope[10] has found for 1,3,5-cyclooctatriene (VIII) and bicyclo [4,2,0] octa-2,4-diene (IX).

VIII IX

Extending their studies, Doering and Knox[11] found that the photochemical or thermal decomposition of ethyl diazoacetate in hydrocarbon solvents gave saturated esters in yields of about 40%. For example,



They concluded that the reaction involved a divalent carbon intermediate which they called a "carbene".

$$N_2CHCOOEt \longrightarrow N_2 + :CHCOOEt \xrightarrow{RH} RCH_2COOEt.$$

As evidence that the intermediate was not a diradical, the authors noted that it showed no preference for a tertiary hydrogen as do free radicals. Also they observed that while ethyl diazoacetate gave ethyl cyclohexaneacetate when heated in cyclohexane, the same reaction in the presence of copper powder gave only diethyl fumarate.

Photochemical Reactions with Polyhalomethanes

Recently Urry and Eiszner[12] have studied the light-induced reactions of diazomethane with polyhalomethanes. These reactions were found to yield polyhaloneopentane derivatives, a methylene group being interposed between each halogen atom in the organic halide and the carbon atom to which it is attached. For example, carbon tetrachloride gave a 60% yield of tetrachloroneopentane together with nitrogen and a small amount of polymethylene. Similar results were obtained with bromotrichloromethane, chloroform and methyl trichloroacetate.

$$CCl_4 + 4\ CH_2N_2 \rightarrow 4\ N_2 + C(CH_2Cl)_4$$

For these reactions a free radical mechanism is suggested by the following observations:

1. It is light-induced.
2. It is inhibited by diphenylamine.
3. It is observed only with organic halides known to undergo free radical addition to olefins.[13]
4. Equal volumes of nitrogen are evolved per unit time at constant light intensity and temperature and hence the reaction is of zero order.

Furthermore a reaction sequence involving stable intermediates as

$$CCl_4 \rightarrow ClCH_2CCl_3 \rightarrow (ClCH_2)_2\ CCl_2 \quad \text{etc.}$$

is most unlikely for the intermediates would have to be far more reactive with diazomethane than carbon tetrachloride which is present in great excess. However, the first intermediate 1,1,1,2-tetrachloroethane did not give this reaction with diazomethane. Also 1,1,1-trichloroethane, the possible first intermediate in the reaction with chloroform, was equally unreactive.

Therefore, the accumulated evidence favors a free radical, chain reaction mechanism involving only unstable intermediates. The following reaction scheme which was proposed for carbon tetrachloride fulfills these conditions by postulating successive free radical rearrangements involving 1,2-shifts of chlorine alternating with reactions with diazomethane. Reactions 1 and 2 are the chain-initiating and reactions 3 to 10 are the chain-propagating steps. No evidence is at present available regarding chain termination.

1. $CH_2N_2 \longrightarrow N_2 + :CH_2$

2. $:CH_2 + CCl_4 \longrightarrow .CH_2Cl + .CCl_3$

3. $.CCl_3 + CH_2N_2 \longrightarrow N_2 + .CH_2CCl_3$

4. $.CH_2CCl_3 \longrightarrow ClCH_2\dot{C}Cl_2$

5. $ClCH_2\dot{C}Cl_2 + CH_2N_2 \longrightarrow ClCH_2\underset{\underset{\cdot CH_2}{|}}{C}Cl_2$

6. $ClCH_2\underset{\underset{\cdot CH_2}{|}}{C}Cl_2 \longrightarrow ClCH_2\dot{C}Cl$ (CH_2Cl)

7. $(ClCH_2)_2\dot{C}Cl + CH_2N_2 \longrightarrow (ClCH_2)_2CCl$ ($\cdot CH_2$)

8. $(ClCH_2)_2\underset{\underset{\cdot CH_2}{|}}{C}Cl \longrightarrow (ClCH_2)_2\underset{\underset{CH_2Cl}{|}}{C}\cdot$

9. $(ClCH_2)_3C\cdot + CH_2N_2 \longrightarrow N_2 + (ClCH_2)_3CCH_2\cdot$

10. $(ClCH_2)_3CCH_2\cdot + CCl_4 \longrightarrow (ClCH_2)_3CCH_2Cl + \cdot CCl_3$

The possible competing reactions of the intermediate free radicals with either diazomethane or organic halide impose stringent requirements if the self-sustaining chain reaction is to occur. Thus, the reactions of methyl chloroacetate and methyl dichloroacetate with diazomethane to give products having a wide boiling range suggest the failure of these compounds to react readily in step 10.

A similar reaction scheme seems generally applicable to the other photochemical reactions of diazomethane which have been discussed.

REFERENCES

1. A. Hantzsch and M. Lehman, Ber., 34, 2522 (1901).
2. T. Curtius, A. Darapsky and E. Muller, ibid., 41, 3168 (1908).
3. H. Meerwein, H. Rathjen and H. Werner, ibid., 75, 1610 (1942).
4. A. Guenther, Ann., 123, 121 (1862).
5. J. U. Nef, ibid., 298, 367 (1897).
6. J. Thiele and F. Dent, ibid., 302, 273 (1898).
7. R. G. W. Norrish and G. Porter, Discussions of the Faraday Soc., No. 2, 97 (1947).
8. W. von E. Doering and L. H. Knox, J. Am. Chem. Soc., 72, 2305 (1950).
9. E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, ibid., 61, 1057 (1939).
10. A. C. Cope, A. C. Haven, Jr., F. L. Ramp and E. R. Trumbull, ibid., 74, 4867 (1952).
11. W. von Doering and L. H. Knox, Abstracts of Papers, 119th Meeting, American Chemical Society, Boston, Mass., April 2, 1951, p. 2M.
12. W. H. Urry and J. R. Eiszner, J. Am. Chem. Soc., 74, 5822 (1952).
13. M. S. Kharasch, E. V. Jensen and W. H. Urry, ibid., 69, 1100 (1947); M. S. Kharasch, O. Reinmuth and W. H. Urry, ibid., 69, 1105 (1947).

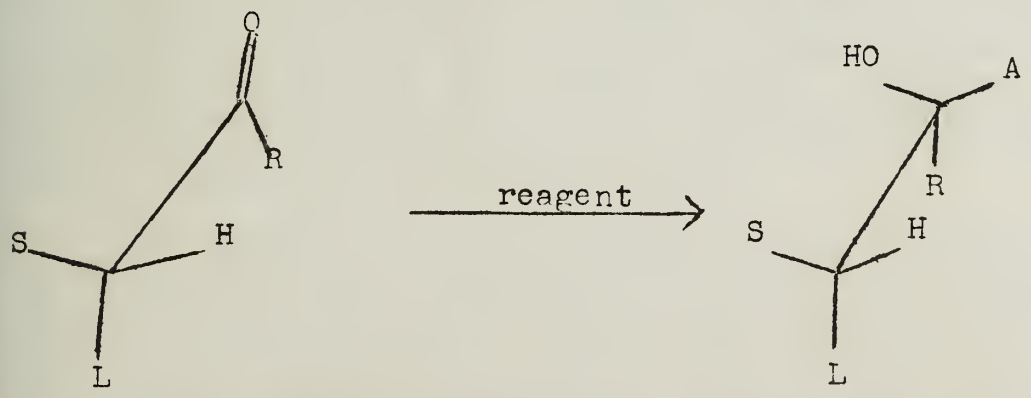
STERIC CONTROL OF ASYMMETRIC INDUCTION

Reported by Moses Passer February 20, 1953

The laboratory synthesis of a new asymmetric center in a molecule already containing (at least) one asymmetric center, with the resulting diastereomers formed in unequal proportions, was first achieved nearly half a century ago,[1] and many instances are now known of such intramolecular asymmetric syntheses.[2,3] An example of intermolecular asymmetric synthesis is afforded by the reaction of benzaldehyde with hydrogen cyanide,[3] which in the presence of quinine gives excess of (+) - mandelonitrile, and in the presence of quinidine excess of the other enantiomorph. The use of an enzyme in the reaction medium[3] is an elegant way to achieve asymmetric induction, and recently asymmetric syntheses have been accomplished through the use of optically-active reducing agents to reduce ketones to active alcohols.[4,5,6,7]

The steric factors involved in asymmetric synthesis have been studied by several investigators. Fieser[8] has proposed certain generalizations that obtain in asymmetric syntheses in steroids, while Hassel,[9] Pitzer,[10] and Barton[11] present evidence suggesting that both in simple cyclohexane systems[9,10] and in cyclohexane-incorporating steriods[11] the preferred configuration on any given asymmetric carbon atom is that in which the more bulky substituent occupies the equatorial position in the chair conformation. This generalization is supported by electron-diffraction studies,[9] thermodynamic calculations,[10] and studies of the relative stability and propensity toward formation of the isomers.[11]

Most recently, and nearly simultaneously, Curtin[12] and Cram[13] have each proposed for the acyclic series a generalization to correlate the relative bulk of substituents on an asymmetric carbon atom <u>alpha</u> to a carbonyl group with the observed stereospecificity of reactions in which the carbonyl undergoes transformation to an asymmetric alcohol. The two versions of the rule essentially state that non-catalytic reactions of the type shown in equation (1) will give rise preponderantly to the indicated diastereomer.



(1)

In Cram's version, the more general of the two, L and S, representing the larger and smaller groups, may be alkyl, aryl, amino or

substituted amino, or hydroxy or substituted hydroxy; R may be hydrogen, alkyl, or aryl; and the reagent may be a Grignard reagent or a reducing agent such as lithium aluminum hydride, aluminum alkoxide, sodium-alcohol, or sodium amalgam. In Curtin's (more limited) version L is methyl or phenyl; S is amino, hydroxy, or methoxy; R is p-substituted phenyl or α-naphthyl; and the reagent is p-substituted phenyl- or α-naphthylmagnesium halide.

Curtin's statement is based on his work with twelve reactions of this general type, in each of which the relative configurations for both reactants and products are known. Cram's broader generalization is based on a study from the literature of twenty-seven such reactions, essentially similar to Curtin's in that in nearly every case group S on the α-carbon is either hydroxy or amino, and on his own work with nine reactions in which the α-substituents are hydrocarbon groupings. In addition, each author calls attention to a number of reactions in which configurations, as yet unknown, can be predicted by the rule and which when established by independent methods will provide tests for the rule.

Certain of the concepts inherent in the rule are applied by Cram (a) to explain the variations in ratio of structural isomers obtained in the reactions of a pair of diastereomers with 3-nitrophthalic anhydride[14] and (b) to account for the difference in rates of the S_N2 reactions of halide ion with the brosylates of a pair of diastereomers.[15]

Two problems arise when a reaction is studied as to its consistency with the rule. One is the matter of yield. Clearly, if only one isomer is isolated and in less than 50% yield, there exists the possibility of its being the less abundant of the two possible products. In Curtin's work the yields in all cases but two are 50% or greater. Cram points out that in most of his examples in which the yields are low the other isomer was obtained in approximately equal yield by reversing the order in which the substituents were introduced. Although not rigorous, this provides reasonable assurance that the isomers isolated, even though in low yield, are indeed predominant. The second, more serious difficulty has to do with the question of relative bulk of groups,[16] especially as the concept is utilized in this particular situation. For example, Cram considers a phenyl effectively more bulky than a dodecylamino because of the greater volume of the former in the immediate vicinity of the reaction center. However, situations are conceivable in which the planarity of a phenyl group would allow it to offer less hindrance to an approaching reagent than would a smaller, but non-planar group.

Cram suggests two explanations for the observed stereospecificity. First, coordination of either the Grignard reagent or of the reducing agent with carbonyl oxygen would tend to increase the effective bulk of the latter and orient it as shown in equation (1), situated between the two least bulky groups of the adjacent carbon. A second explanation is analagous to the cyclic intermediate proposed by Doering[5] for his stereospecific Meerwein-Ponndorf-Verley reduction of a ketone by optically-active 2-butanol.

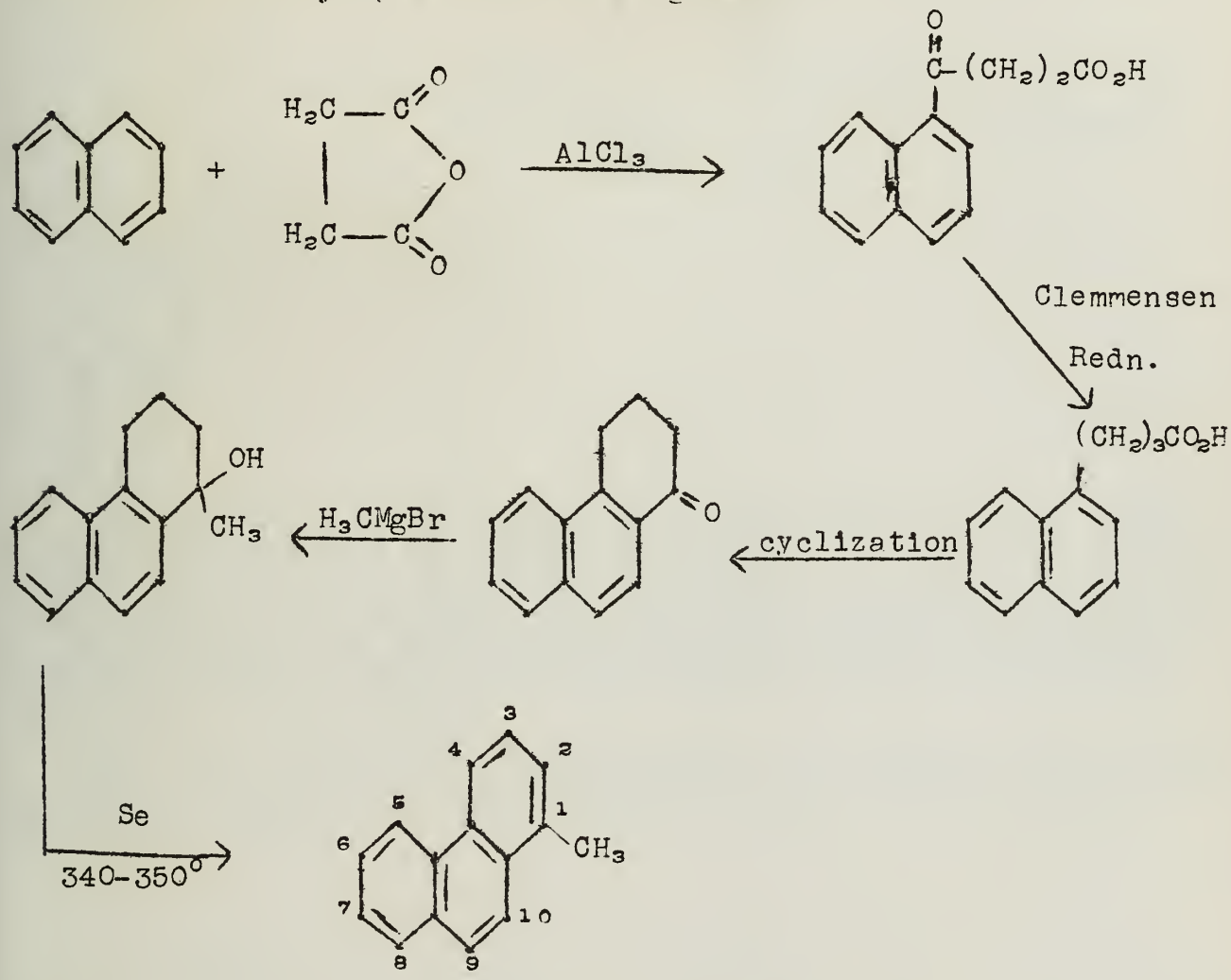
REFERENCES

1. A. McKenzie, J. Chem. Soc., 85, 1249 (1904).
2. E. E. Turner and M. M. Harris, Quarterly Reviews, 1, 299 (1947).
3. R. L. Shriner, R. Adams, and C. S. Marvel, in "Organic Chemistry," H. Gilman, editor, John Wiley and Sons, Inc., New York, second edition, 1943, volume I, pp. 308-315.
4. W. von E. Doering and T. C. Aschner, J. Am. Chem. Soc., 71, 838 (1949).
5. W. von E. Doering and R. W. Young, ibid., 72, 631 (1950).
6. H. S. Mosher and E. La Combre, ibid., 72, 3994, 4991 (1950).
7. A. Bothner-By, ibid., 73, 846 (1951).
8. L. F. Fieser, Experientia, 6, 312 (1950).
9. (a) O. Hassel and H. Viervoll, Acta. chem. Scand., 1, 149 (1947); (b) O. Hassel and B. Ottar, ibid., 1, 929 (1947); (c) O. Bastiansen, O. Ellerson, and O. Hassel, ibid., 3, 918 (1949).
10. C. W. Beckett, K. S. Pitzer, and R. Spitzer, J. Am. Chem. Soc., 69, 2488 (1947).
11. D. H. R. Barton, Experientia, 6, 316 (1950).
12. D. Y. Curtin, E. E. Harris, and E. K. Meislich, J. Am. Chem. Soc., 74, 2901 (1952).
13. D. J. Cram and F. A. Abd Elhafez, ibid., 74, 5828 (1952).
14. Idem, ibid., 74, 5846 (1952).
15. Idem, ibid., 74, 5851 (1952).
16. (a) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, second edition, 1940, p. 164; (b) reference (3), first edition, 1938, volume I, p. 268.

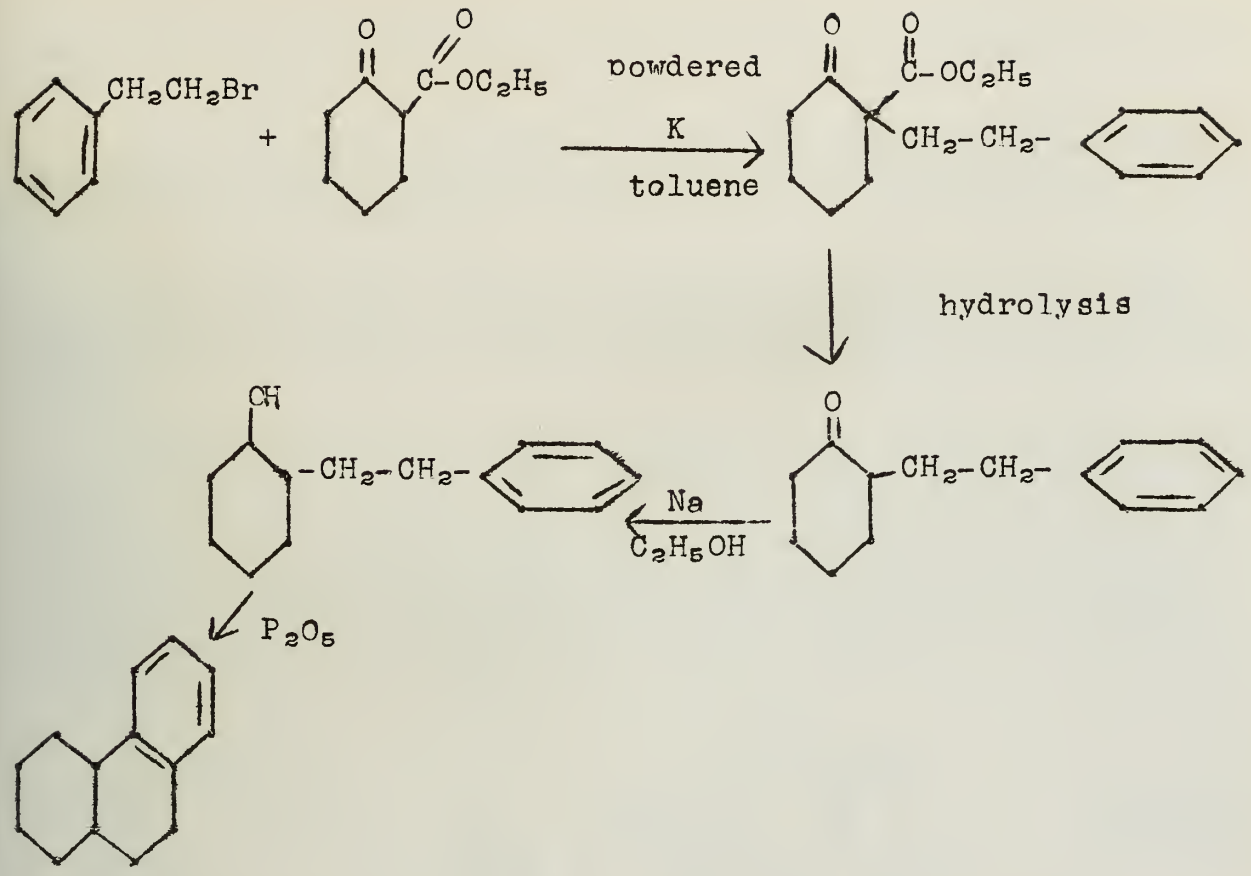
SYNTHESIS OF PHENANTHRENES

Reported by C. W. Hinman February 27, 1953

In 1932 Haworth[1] developed a synthesis which has provided many of the substituted phenanthrenes in good yields. The method involves initially the reaction of an acid anhydride or acyl chloride with naphthalene in the presence of aluminum trichloride. The treatment thereafter depends largely upon the derivative desir As an illustration of its use the reaction sequence for the production of 1 methyl phenanthrene is given.

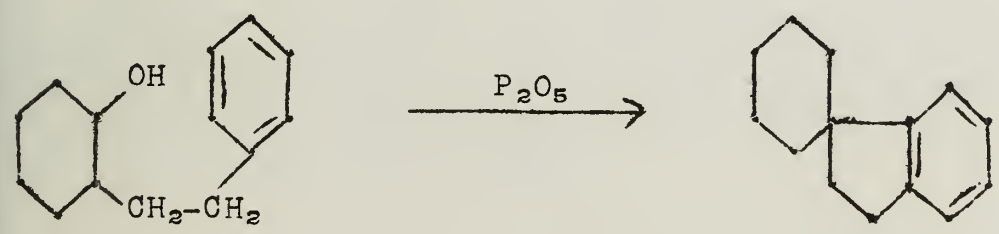


Much of the recent work done on phenanthrenes has been based on the method of synthesis first used by Bardham and Sengupta.[2] This synthesis involves the alkylation of a carbethoxycyclohexanone followed by hydrolysis and cyclization.



The product obtained proved to be 1,2,3,4,4a,9,10,10a octahydrophenanthrene and by aromatization with selenium at 280-340° C, yielded phenanthrene. By proper substitution of either the cyclohexane ring, or the benzene ring many other octahydrophenanthrenes can be obtained. By treating the 2-β phenyl ethyl cyclohexanone with the Grignard reagent an angular methyl group has been introduced into the 4a position.[3]

The chief objection to this synthesis of octahydrophenanthrene is that the cyclization step produces a spirane to the extent of 50 - 60 per cent.



Bogert found that by reacting certain carbinols with concentrated sulfuric acid octahydrophenanthrenes could be produced which were identical with those made by Bardham and Sengupta.[4]

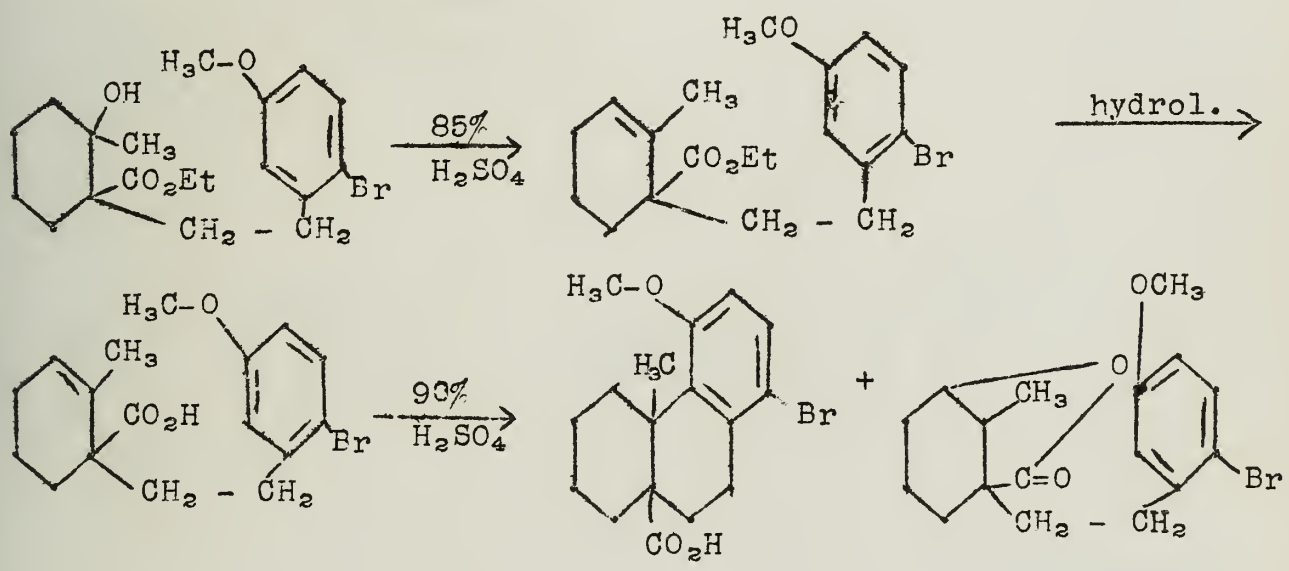
He was able to overcome the spirane formation, however, by using beta-phenylethyl-2 methyl cyclohexanol. He obtained almost

exclusively the 4a-methyl-1,2,3,4,4a,9,10,10a, octahydrophenanthrene.

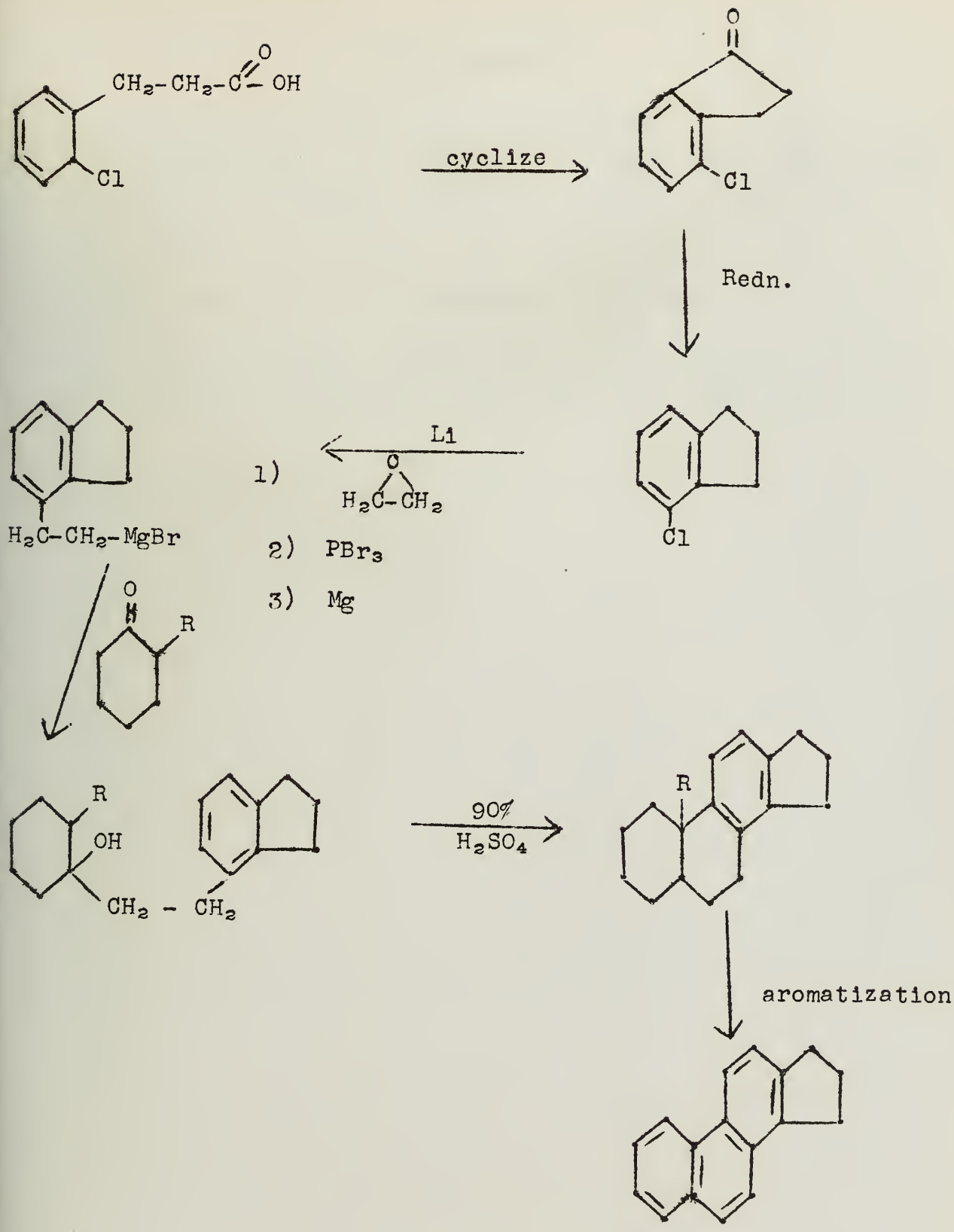
Cook has shown conclusively that the octahydrophenanthrene obtained by either the Bardham-Sengupta or the Bogert method is a mixture of two isomers.[5]

Barnes has shown that if an angular methyl group is introduced the resulting 4a methyl, 1,2,3,4,4a,9,10,10a octahydrophenanthrene has but one form, which he believes to be the trans isomer.[6]

Introduction of an angular methyl group actually facilitates the cyclization step in these syntheses, but introduction of an angular carboxyl group gives rise to new difficulties. When the cyclization step is attempted with 85% sulfuric acid only dehydration takes place. Only after hydrolysis of the ester and treatment with 90% sulfuric acid is any of the desired cyclic product obtained, and even then lactone formation is the favored reaction.[7]



The usual procedure for synthesizing compounds having a cyclopentanophenanthrene nucleus has been carried out by building up ring C and D starting with a substituted benzene or naphthalene. A new approach, most used by Barnes, starts with a hydrindene and adds to it the A and B rings.[8]



The products of cyclization were proved to be cyclization products by oxidation with dil.HNO_3 which yielded 1,2,3,4 tetra carboxybenzene.

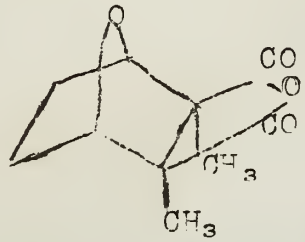
BIBLIOGRAPHY

1. R. D. Haworth, J. Chem. Soc., 1125 (1932).
2. J. C. Bardham and S. C. Sengupta, J. Chem. Soc., 2520 (1932).
3. J. C. Bardham and S. C. Sengupta, J. Chem. Soc., 2798 (1932).
4. D. Perlman, D. Davidson, and M. T. Bogert, J. Org. Chem. 1, 288 (1936).
5. J. W. Cook, C. L. Hewett, and A. M. Robinson, J. Chem. 168 (1939).
6. R. A. Barnes and R. T. Gottesman, J. Am. Chem. Soc., 74, 35 (1952).
7. R. A. Barnes, H. P. Hirschler, B. R. Bluestein, J. Am. Chem. Soc., 74, 32 (1952).
8. R. A. Barnes, L. Gordon, J. Am. Chem. Soc., 71, 2644 (1949).

THE SYNTHESIS OF CANTHARIDIN

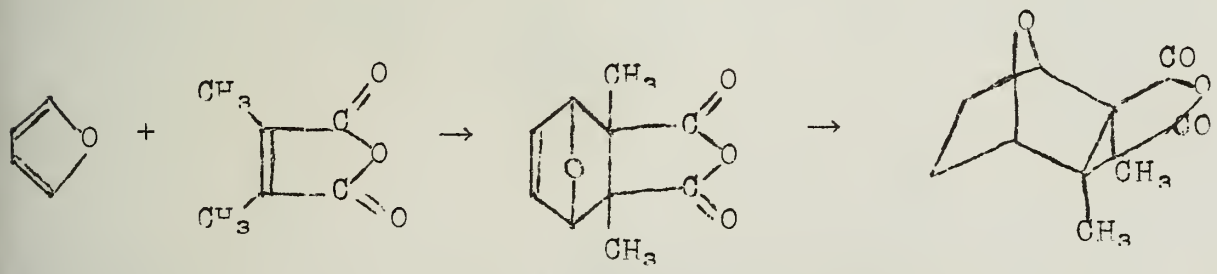
Reported by Elliott E. Ryder February 27, 195:

Cantharidin was first obtained as a crystalline substance in 1810 by Robiquet, and in 1914 the following structure was suggested by Gadamer and co-workers.



A number of attempts have been made throughout the years to synthesize this compound, however, an acceptable method was not developed until recently.

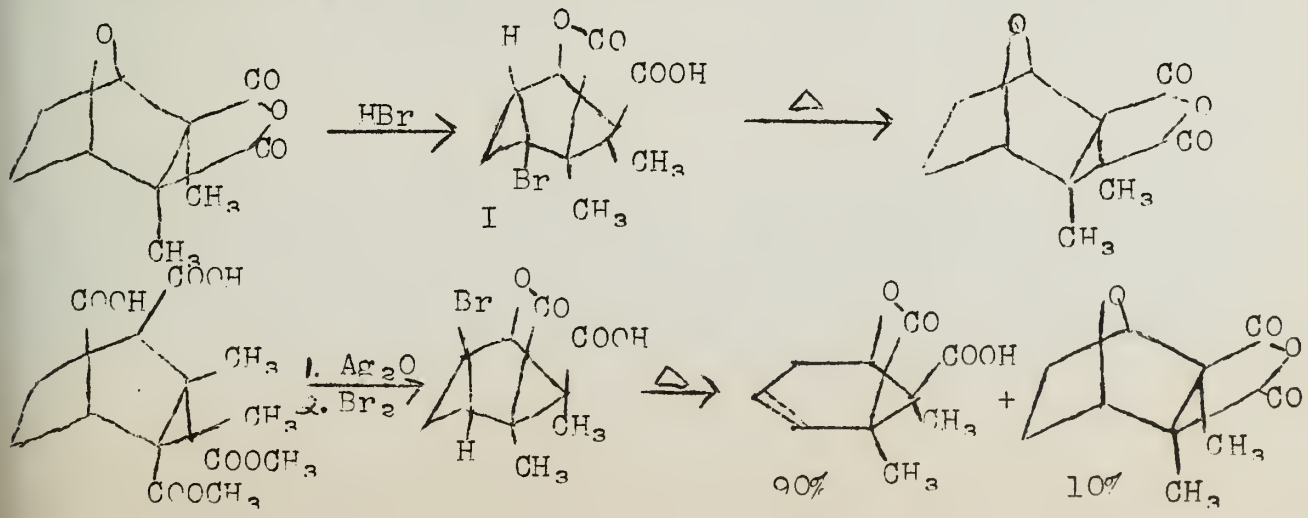
In 1928 von Bruchhausen and Bersch attempted the following condensation,[1]



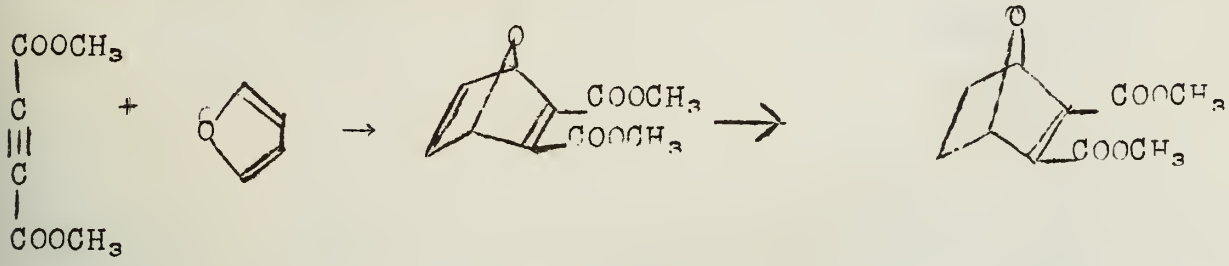
however, it was found that dimethylmaleic anhydride would not enter into a Diels-Alder reaction with this diene.

Attempts to methylate the hydrogenated addition product of maleic anhydride and furan failed to produce the desired compound.[2]

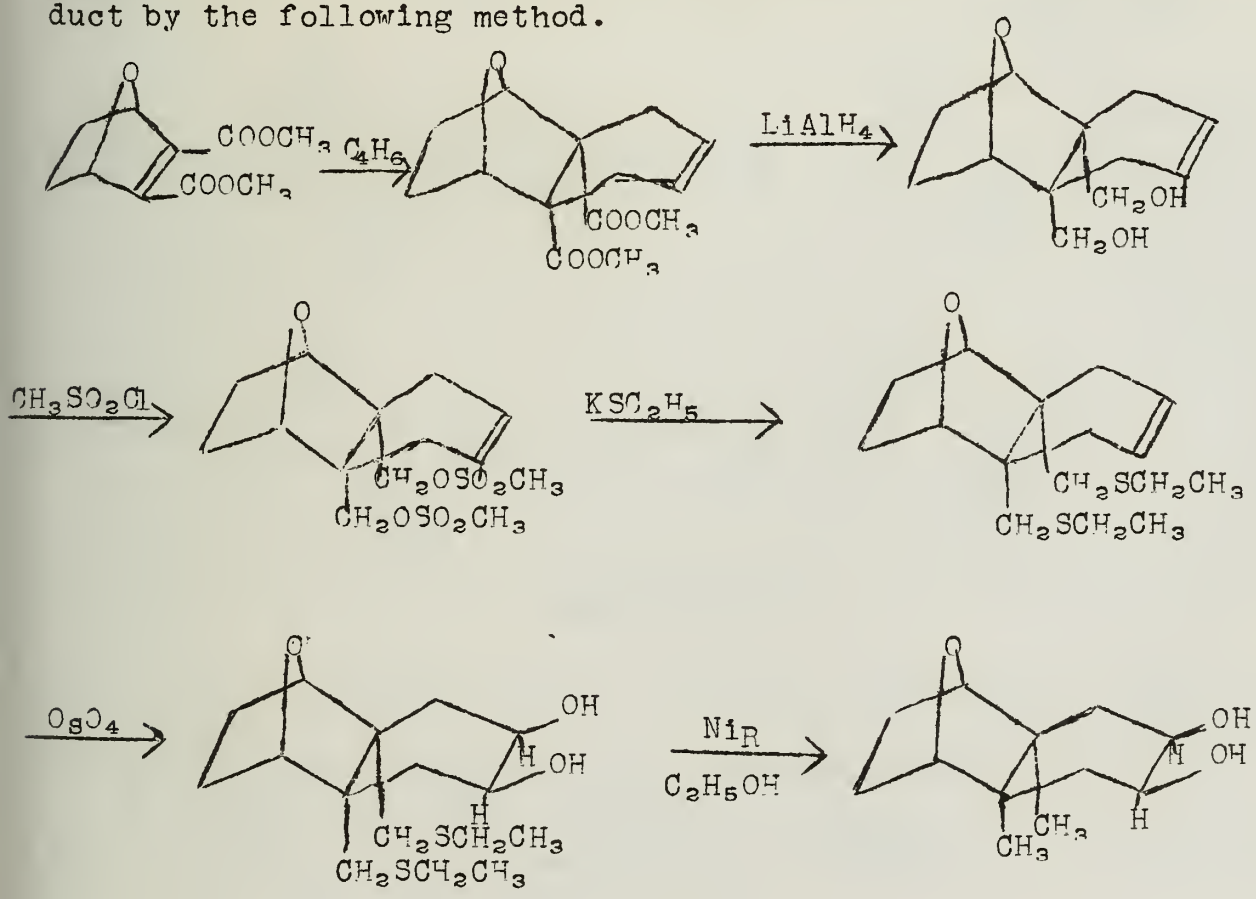
Pyrolysis of hydrobromocantharic acid, I, was shown to reform cantharidin in good yield[3], so Ziegler and co-workers attempted to synthesize this bromoacid.[2] As is shown, their synthesis produced the epimer of hydrobromocantharic acid; though pyrolysis of this compound produced cantharidin in small yield, it may be looked upon as its first total synthesis.



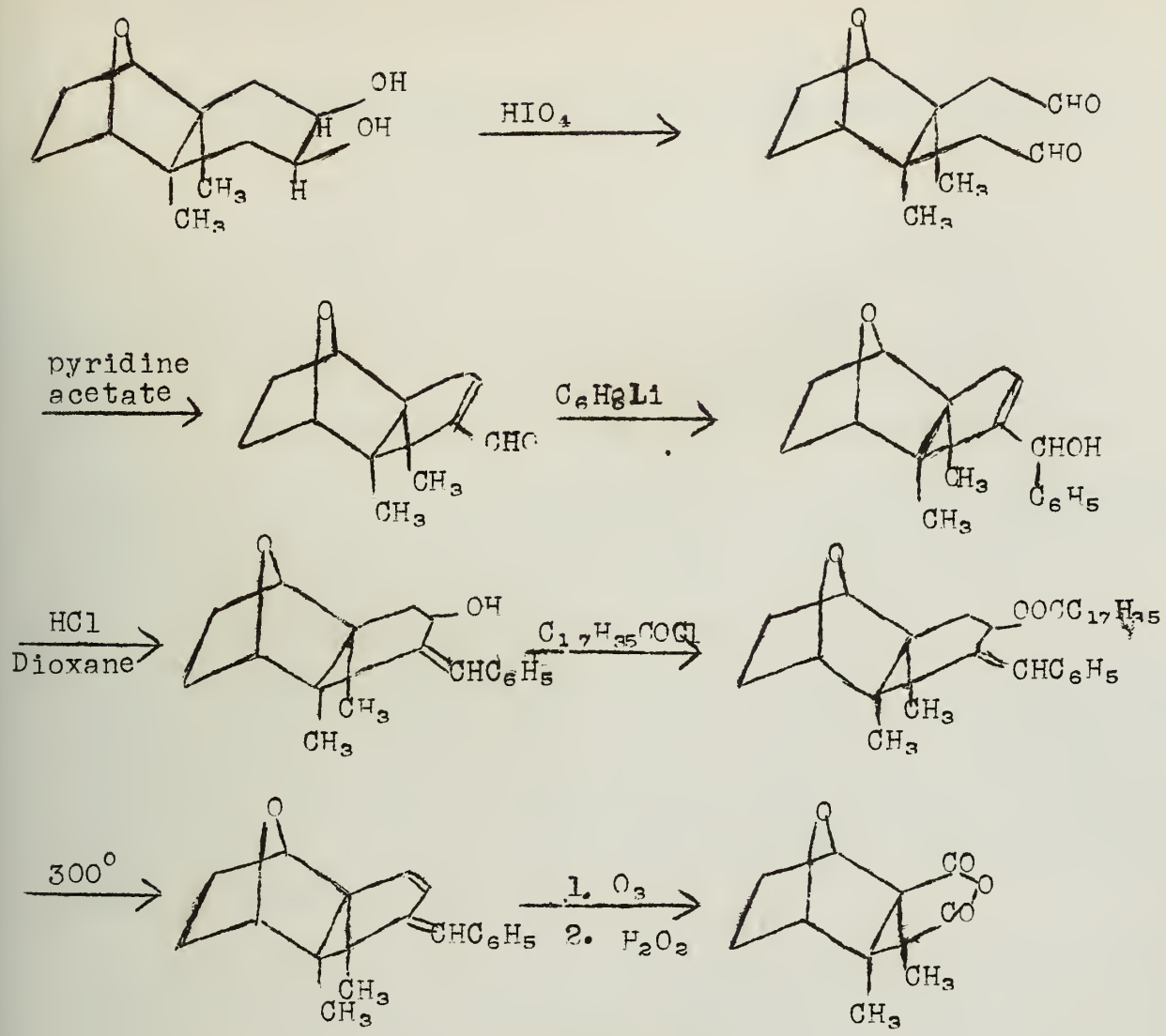
The synthesis which is the subject of this seminar has as its initial step the Diels-Alder condensation of dimethyl acetylenedicarboxylate with furan.[4]



Butadiene was then added to the latter compound, and the ester groups were transformed into the methyl groups of the desired product by the following method.



This glycol was then oxidized to the dialdehyde which was caused to undergo an intramolecular aldol condensation to a cyclopentenealdehyde; treatment of this compound with phenyl lithium followed by pryolysis of the stearate of the rearranged alcohol produced a diene which was then ozonized to yield cantharidin.



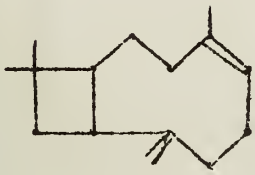
BIBLIOGRAPHY

1. F. von Bruchhausen and H. W. Bersch, Arch. Pharm., 266, 697 (1928).
2. K. Ziegler, G. Schenck, E. W. Krockow, A. Siebert, A. Wenz, and H. Weber, Ann., 551, 1 (1942).
3. S. Gadamer, Arch. Pharm., 252, 636 (1914).
4. G. Stork, E. E. van Tamelen, L. J. Friedman, A. W. Burgstahler, J. Am. Chem. Soc., 75, 384 (1953).

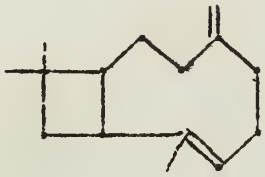
HUMULENE

Reported by W. S. Anderson March 6, 1953

Two sesquiterpenes from clove oil, ~~α~~ and β-caryophyllene, have been assigned the structures given below.[1]



β-caryophyllene



γ-caryophyllene

Until recently, little was known of the structure of α-caryophyllene (known also as humulene), a third sesquiterpene ($C_{15}H_{24}$) in clove oil and a major constituent of hop oil.[2,6]

Evidence for the presence of only one ring

The unsaturation in any compound $C_{15}H_{24}$ can be accounted for by 1) four double bonds 2) three double bonds and one ring 3) two double bonds and two rings 4) one double bond and three rings 4) four rings 5) combinations involving triple bonds with fewer than three double bonds. Hydrogenation, perbenzoic acid titration with analysis of the epoxide, and infrared show the presence of three double bonds. A single ring, therefore, must be present in humulene.

Ozonolysis of tetrahydrohumulene, which according to the infrared data has an endocyclic double bond (967 cm.$^{-1}$), yields a C_{15} dicarboxylic acid. This ozonolysis product, which contains the same number of carbon atoms as the starting material, confirms the presence of a ring.

The hydrohumulenes

The hydrogenated derivatives of humulene have been prepared in an effort to determine the humulene structure.[7] The methods of preparation are outlined in Table 1.

The gem-dimethyl group

Oxidation of humulene ozonide gives α,α-dimethyl succinic acid.[6] From the oxidation of β-dihydrohumulene, α,α-dimethyl succinic acid and β,β-dimethyl adipic acid can be isolated, leaving no doubt that a structure of the following type is present:

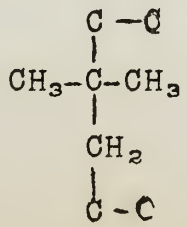
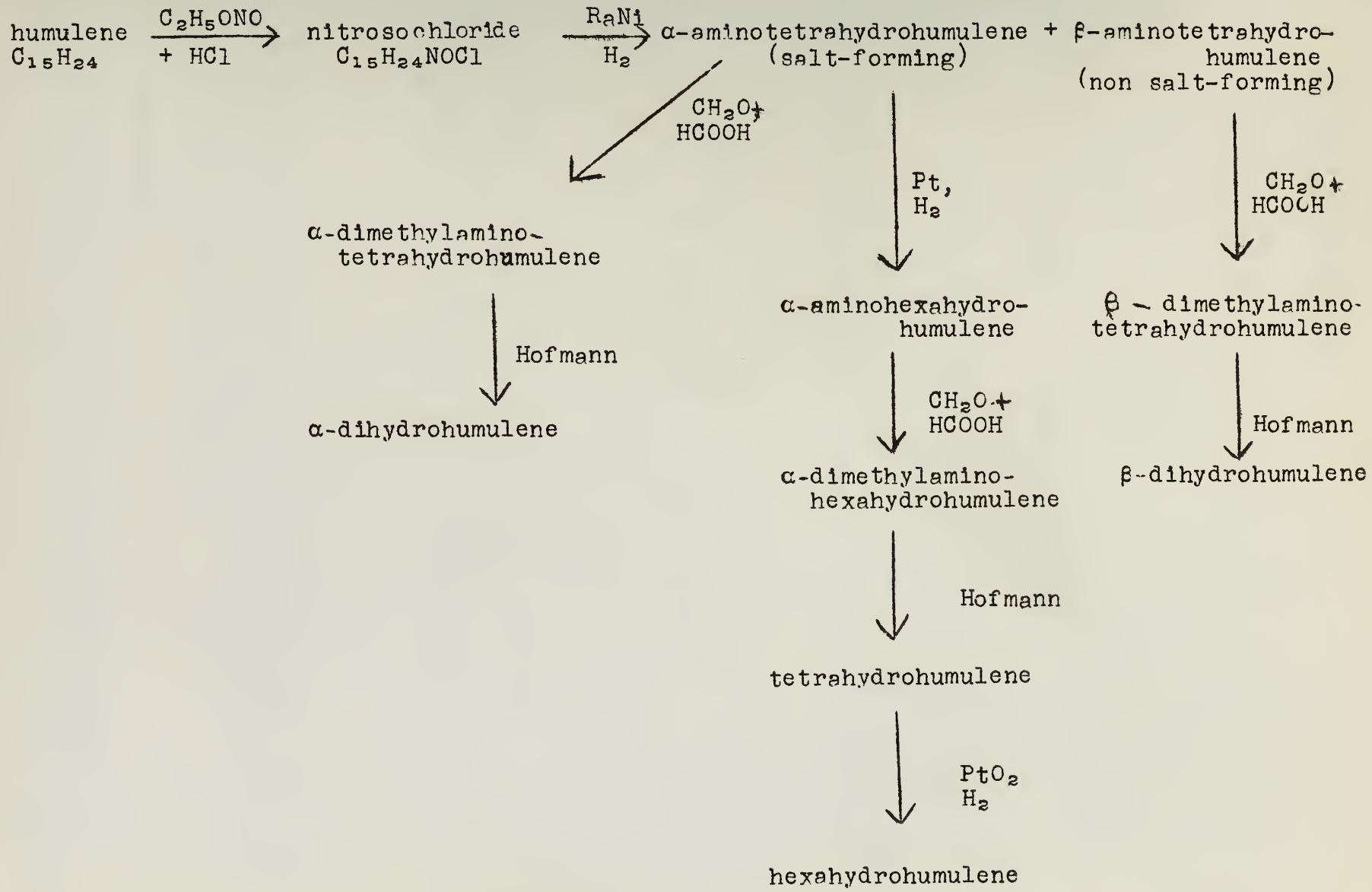


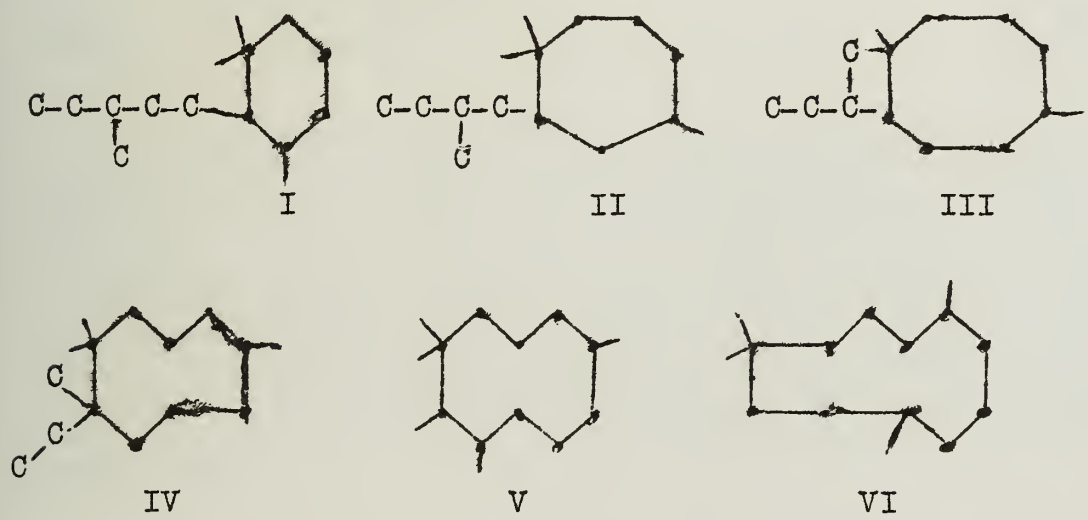
Table I


humulene
$C_{15}H_{24}$
C_2H_5ONO
+ HCl
nitrosochloride
$C_{15}H_{24}NOCl$
RaNi
H_2
α-aminotetrahydrohumulene
(salt-forming)
+
β-aminotetrahydro-
humulene
(non salt-forming)
CH_2O+
HCOOH
α-dimethylamino-
tetrahydrohumulene
Hofmann
α-dihydrohumulene
Pt,
H_2
α-aminohexahydro-
humulene
CH_2O+
HCOOH
α-dimethylamino-
hexahydrohumulene
Hofmann
tetrahydrohumulene
PtO_2
H_2
hexahydrohumulene
CH_2O+
HCOOH
β - dimethylamino-
tetrahydrohumulene
Hofmann
β-dihydrohumulene

The size of the ring

If one assumes that the gem-dimethyl group is located on a ring carbon atom, then that ring must be at least six-membered to explain the β,β-dimethyl adipic acid oxidation product. The C_{15} dicarboxylic acid obtained by ozonolysis forms an anhydride when treated with acetic anhydride, but does not form a ketone when its thorium salt is heated. A six-membered ring should give on ozonolysis a ketonizable acid; therefore, the gem-dimethyl group, if on a ring, is on a large ring. Infrared also gives no support to the six-membered ring structure; 1000 cm^{-1} and 1055 cm^{-1} peaks are missing.

Levulinic aldehyde is another humulene ozonolysis product. If one now assumes that humulene, like other cyclic sesquiterpenes, has its isoprene units linked head-to-tail as in the farnesene chain, that it is a single substance or a mixture of substances differing only in the position of the double bonds, and that the gem-dimethyl group is on a cyclic carbon atom, then only carbon skeletons I through VI can be written for humulene.[7]



I has been synthesized;[4] it is not hexahydrohumulene, a fact which supports the absence of a six-membered ring. Skeletons II-V cannot afford both levulinic aldehyde and α,α-dimethyl succinic acid as degradation products. Structure VI is left as the carbon skeleton for humulene.

The double bonds

Indications that the double bonds in humulene are not conjugated are 1) failure of the Diels-Alder reaction of α-dihydrohumulene with maleic anhydride 2) failure of sodium and alcohol reduction 3) ultraviolet absorption only below 2350 Å 4) absence of an exaltation of molecular refraction. The evidence is not conclusive, however, since conjugated double bonds in large rings do not behave normally. 1,3-cyclooctadiene,

for example, does not form a simple adduct with maleic anhydride.

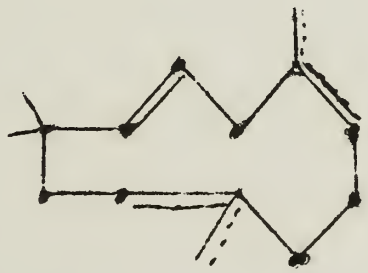
Ozonolysis yields formaldehyde as well as levulinic aldehyde an observation indicating a terminal methylene group.

Infrared data are given in Table II.

Table II

Frequency	Assignment	Where present			
		Humulene	β-Dihydro	Tetrahydro	Hexahydro
1360	CH_3	X	X	X	X
1450	$-CH_2-$	X	X	X	X
967	trans $RCH=CHR'$	X	X	X	-
840 doublet 831	$RCH=CR'R''$ (two types)	X	X	-	-
885	$CH_2=CRR'$	X	X	-	-

The presence of four double bond frequencies in humulene and in β-dihydrohumulene is explained if these substances are mixtures of isomers having the double bonds in different positions. A 1,5,8 arrangement of double bonds in humulene for example, would account for obtaining levulinic aldehyde and α,α-dimethylsuccinic acid. However, an exocyclic double bond is required to obtain formaldehyde, which has been obtained in 96% of the yield expected from one exocyclic double bond. The existence of more than one isomer is, therefore, a strong possibility, and the best representation which can be made[7] for humulene is



This large ring can easily accommodate the endocyclic trans double bond indicated by infrared; the model is compact and strainless; and finally, the observed (probably spurious) optical activity $[\alpha]_D^{20} = 1.00°$ is compatible with this structure.[5]

REFERENCES

1. John Walker, Organic Chem. Seminars, University of Illinois, March 21, 1952.
2. V. Herout, M. Streibl, J. Mleziva, and F. Šorm, Coll. Czech. Chem. Comm., 14, 716 (1949).
3. F. Šorm, J. Mleziva, Z. Arnold, J. Plíva, ibid., 14, 699 (1949).
4. F. Šorm and L. Dolejs, ibid., 15, 96 (1950).
5. F. Šorm, M. Streibl, J. Plíva, V. Herout, Chem. Listy, 45, 308 (1951); [CA 46, 4497 (1952)].
6. G. R. Clemo and J. O. Harris, J. Chem. Soc., 1951, 22.
7. G. R. Clemo and J. O. Harris, ibid., 1952, 665.
8. G. R. Clemo and J. O. Harris, Chem. and Ind., 1951, 50.
9. G. R. Clemo and J. O. Harris, ibid., 1951, 799.
10. M. L. Wolfrom and A. Mishkin, J. Am. Chem. Soc., 72, 5350 (1950).
11. Atsushi Fujita and Yosho Hirose, J. Pharm. Soc. Japan 71, 176 (1951); [CA 45, 6804 (1951)].

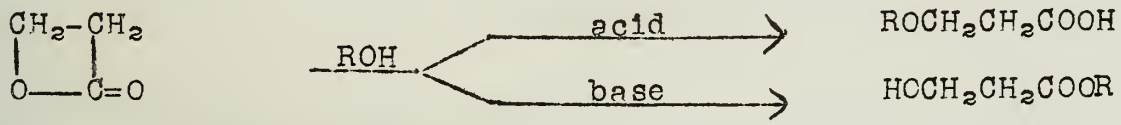
NEW REACTIONS OF β-PROPIOLACTONE

Reported by William S. Friedlander March 6, 1953

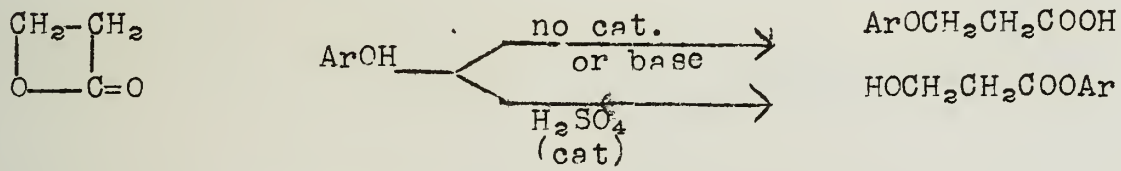
Propiolactone, well established as a synthetic tool in organi chemistry, owes its utility to the fact that it is a β-lactone. While γ and δ lactones usually undergo normal ester hydrolysis, it is not difficult with propiolactone, by using appropriate conditions, to obtain cleavage of the β-carbon-oxygen bond. Some authors[1,8] have attributed this reaction path to the strain in this bond due to the size of the ring.

A summary of the main reactions of propiolactone follows:[2]

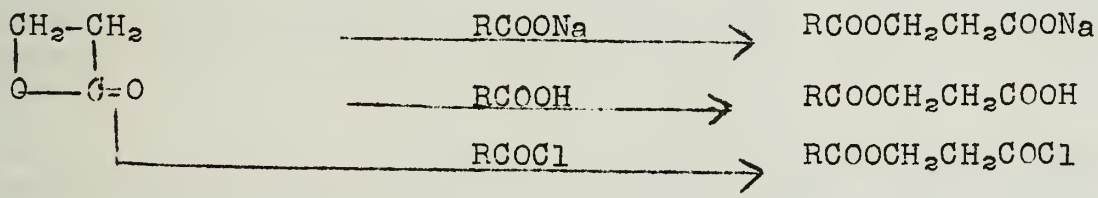
1) Reaction with alcohols:[3]



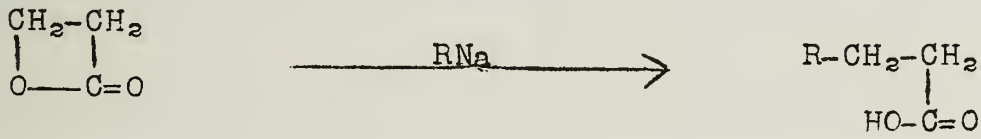
2) Reaction with phenols:[4]



3) Reaction with carboxylic acids,[5] carboxylic acid salts,[6] and acid chlorides.[5]

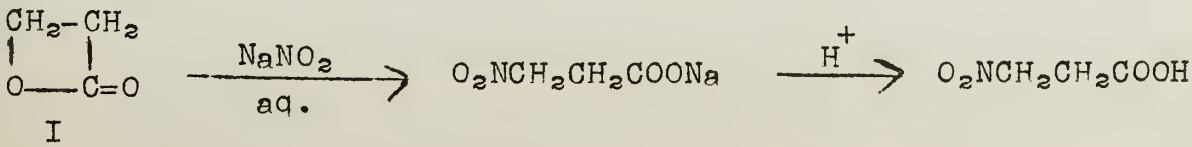


4) Active methylene compounds.[7]



5) Reaction with sodium nitrite, sodium dithionite, sodium cyanide, sodium thiocyanate, sodium succinimide and aryl sulfinic acid salts:[13]

a)



b) $2(I) + Na_2S_2O_4 \longrightarrow \begin{matrix} CH_2CH_2COONa \\ | \\ S_2O_4 \\ | \\ CH_2CH_2COONa \end{matrix} \xrightarrow[\Delta]{H^+} SO_2(CH_2CH_2COOH) + SO_2$

c) $I + NaCN \longrightarrow NCCH_2CH_2COONa \xrightarrow{H^+} NCCH_2CH_2COOH$

(conc. aq. soln.)

d) $I + NaSCN \xrightarrow{aq.} NCSCH_2CH_2COONa \longrightarrow H_2N-\overset{O}{\overset{\|}{C}}-S-CH_2CH_2COOH$

e) $I + C_6H_5SO_2Na \xrightarrow{aq.} C_6H_5SO_2CH_2CH_2COONa \xrightarrow{H^+} C_6H_5SO_2CH_2COOH$

f) $I + \begin{matrix} CH_2-CO \\ | \\ CH_2-CO \end{matrix}\!\!>NNa \xrightarrow{aq.} \begin{matrix} CH_2-CO \\ | \\ CH_2CO \end{matrix}\!\!>NCH_2CH_2COONa \xrightarrow{H^+} \begin{matrix} CH_2-CO \\ | \\ CH_2-CO \end{matrix}\!\!>NCH_2CH_2COOH$

In all the reactions mentioned above it is to be noted that time, temperature, order of mixing, pH, and type of reactant are important factors in determining the course of the reaction and the final product. In some of the reactions, such as with alcohols for example, some generalizations can be made, but the behavior of the amines, particularly of the aliphatic amines, is very unpredictable.

Recently, in order to test the generality of a mechanism[9] for the reactions of alcohols in basic solution with propiolactone Hurd and Hayao[1] have studied the reactions of some substituted anilines with propiolactone. Their findings as well as those in Gresham's earlier work with amines and propiolactone[10] are summarized below.

General reaction:

$$\begin{matrix} CH_2-CH_2 \\ | \quad\;\; | \\ O\!\!-\!\!C=O \end{matrix} \xrightarrow{R_3N} \begin{cases} R_2NCH_2CH_2COOH \\ HOCH_2CH_2CONR_2 \end{cases}$$

R's=H, alkyl, Aryl (except tertiary)

1.) There is no correlation between the basic strength of primary and secondary amines and the amount of amino acid formation. Thus ammonia, dimethylamine, and ethylamine give mostly amino acid, while methylamine, diethylamine and propylamine give mostly amides.

2.) Aromatic or cyclohexylamines give amino acids more consistently than alkylamines.

3.) Usually water is the best solvent for amide formation; and acetonitrile is best for promoting amino acid formation.

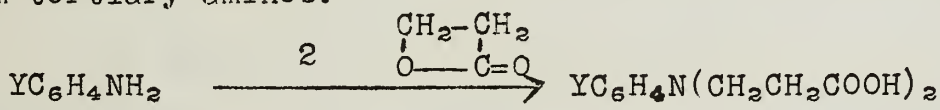
4.) The order of mixing is important here. Thus when dimethylamine is added to the lactone in ether the amino acid is formed. But when the lactone is added to the amine, the amide is the main product; and when the two are added simultaneously to ether the amino acid and amide are produced in about equal proportions.

5.) When substituted anilines are used, the only products formed are B-(anilino)-propionic acids.[1]

Y=COOH, COOEt, SO_3H, SO_2NH_2, Cl, Br, NO_2

a.) The course of these reactions is unaffected by sulfuric acid, sodium ethoxide, or whether the solvent is water, acetone or acetonitrile.

6.) Primary amines will react with two moles of lactone to form tertiary amines:



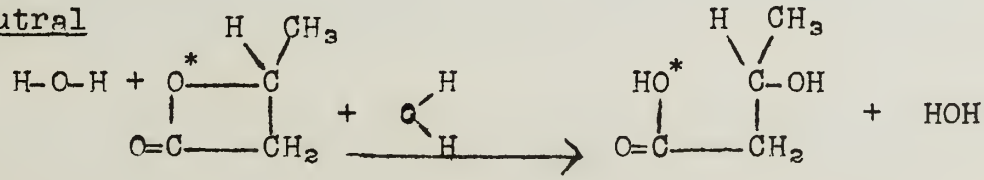
Y=m-COOEt, p-COOEt, p-Cl

7.) In general the reactions of amines with propiolactone are almost quantitative in contrast to reactions with alcohols or acids where there is a good deal of polyester formation observed.

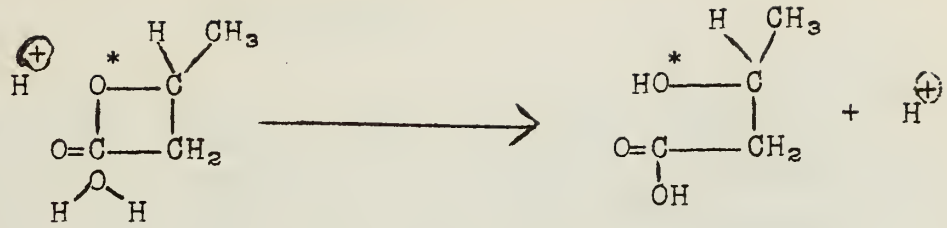
Mechanism:

In general the hydrolysis of a lactone can proceed by three possible mechanisms separately or simultaneously, depending upon the pH of the medium.[11,12]

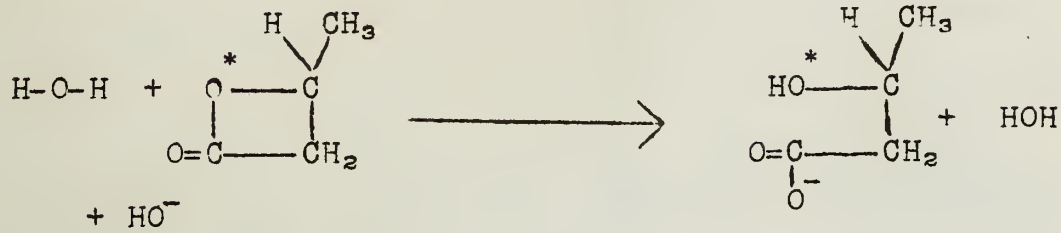
1.) Neutral



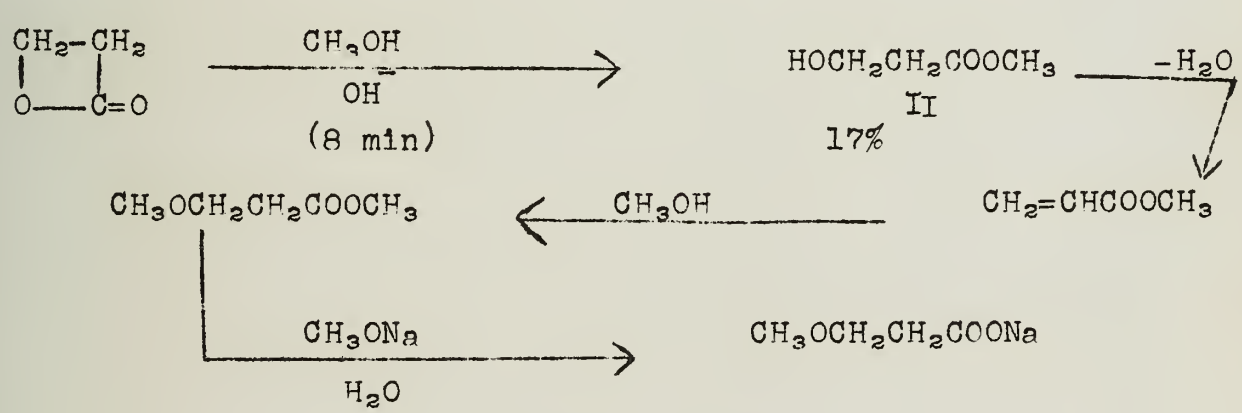
2.) Acidic



3.) Basic



When alcohols or phenols are present, the reaction must also take one of these courses. Bartlett and Rylander[8] have shown that the methanolysis of propiolactone in basic media takes the following course:



If the hydroxy ester (II) is substituted for propiolactone, the same product is formed.

The initial attack by methoxide is in agreement with mechanism 3 above. Since phenoxides are <u>less</u> basic than alkoxides the mechanism of their reaction is of type 1, and the nucleophilic attack by the phenoxide is at the B-carbon.

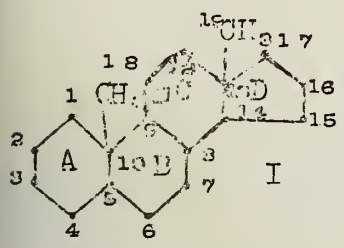
Because the reaction with amines involves basic conditions, one would expect type 3 mechanisms to prevail when they react with propiolactone and the same type of intermediates as with the methanol reaction should be present. However, none of these could be isolated and the course of the reaction appears to be different from type 3.

BIBLIOGRAPHY

1. C. D. Hurd and Shin Hayao, J. Am. Chem. Soc., 74, 5889 (1952).
2. W. E. Smith, Organic Seminar, Spring Semester, 1951.
3. T. L. Gresham, J. E. Jansen, F. W. Shaver, J. T. Gregory, and W. L. Beears, J. Am. Chem. Soc., 70, 1004 (1948).
4. T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, W. I Beears and Marie G. Prendergast, ibid., 71, 661 (1949).
5. T. L. Gresham, J. E. Jansen and F. W. Shaver, ibid., 72, 72 (1950).
6. T. L. Gresham, J. E. Jansen, F. W. Shaver and J. T. Gregory ibid., 70, 999 (1948).
7. T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Fredrick and W. L. Beears, ibid., 73, 2345 (1951).
8. P. D. Bartlett and G. Small, Jr., ibid., 72, 4867 (1950).
9. P. D. Bartlett and P. N. Rylander, ibid., 73, 4273 (1951).
10. T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert and F. T. Fiedorek, ibid., 73, 3168 (1951).
11. A. R. Olson and R. J. Miller, ibid., 60, 2687 (1938).
12. A. R. Olson and J. F. Hyde, ibid., 63, 2459 (1941).
13. T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Frederick, F. T. Fiedorek, R. A. Bankert, J. T. Gregory and W. L. Beears, ibid., 74, 1323 (1952).

11-OXYGENATION OF THE RING-C-UNSUBSTITUTED STEROID NUCLEUS

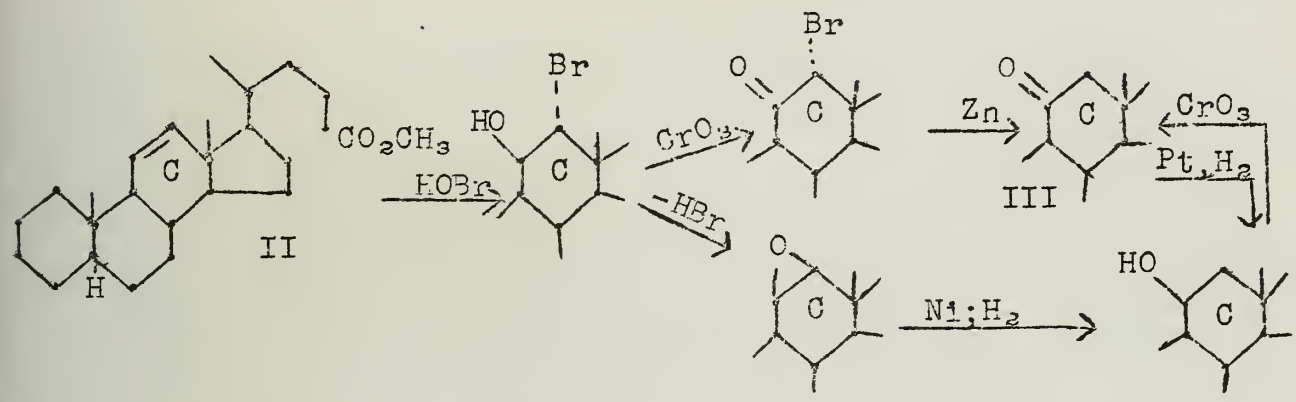
Reported by Howard J. Burke March 13, 1953



I

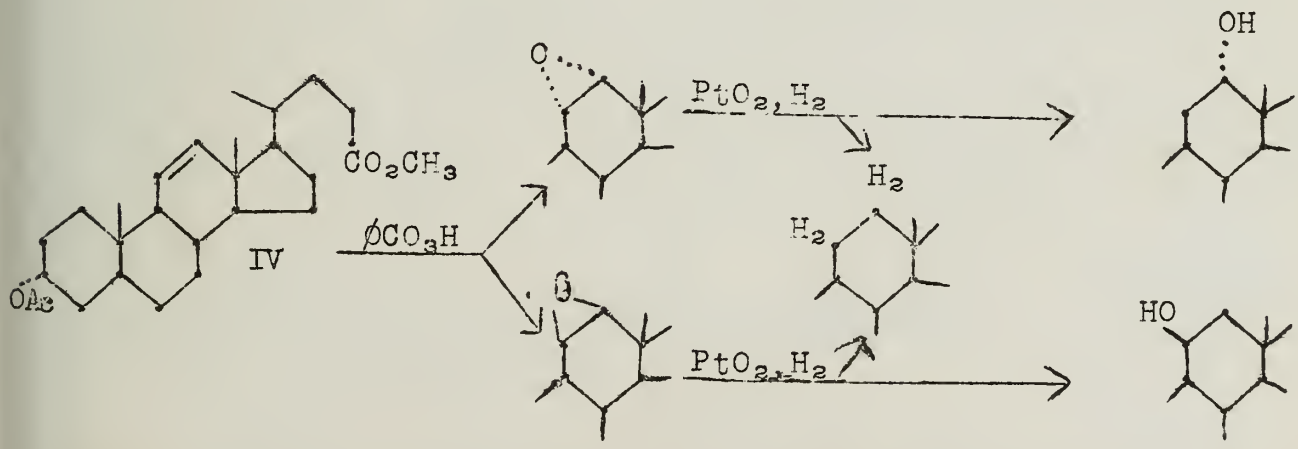
In recent years many ways, both chemical and microbiological, of oxygenating the 11-position of ring-C-unsubstituted steroid nuclei have been developed. The chemical methods all have in common the fact that they use as starting material a steroid having unsaturation somewhere in ring C. These methods are:

A. HOBr-CrO_3[1]. Methyl Δ^{11}-cholenate (II) yields methyl 11-keto-cholanate (III)[1]:

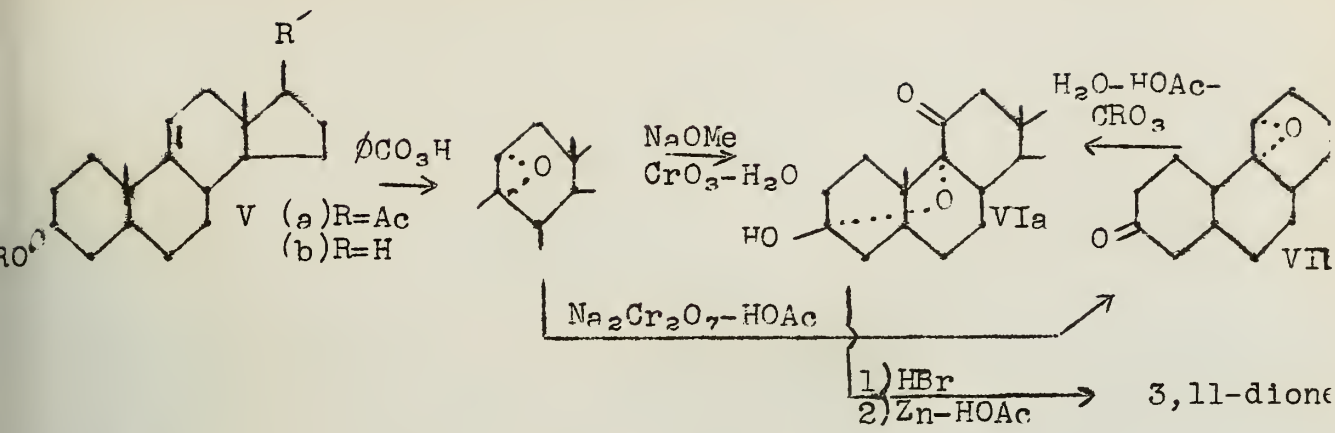


In the original paper the spatial configurations at C_{11} and C_{12} were just the reverse, but the conclusion was reached some years later[40] that the assignment of the β-orientation to the C_{12} substituent of the parent compound was in error. Accordingly, the orientations have been corrected, bringing the results into line with more recent work.

B. Peracids.[2,4-8,10-12,14,18,19,21] The reaction of an 11,12 double bond is shown with methyl Δ^{11}-lithocholenate acetate (IV)[2]:

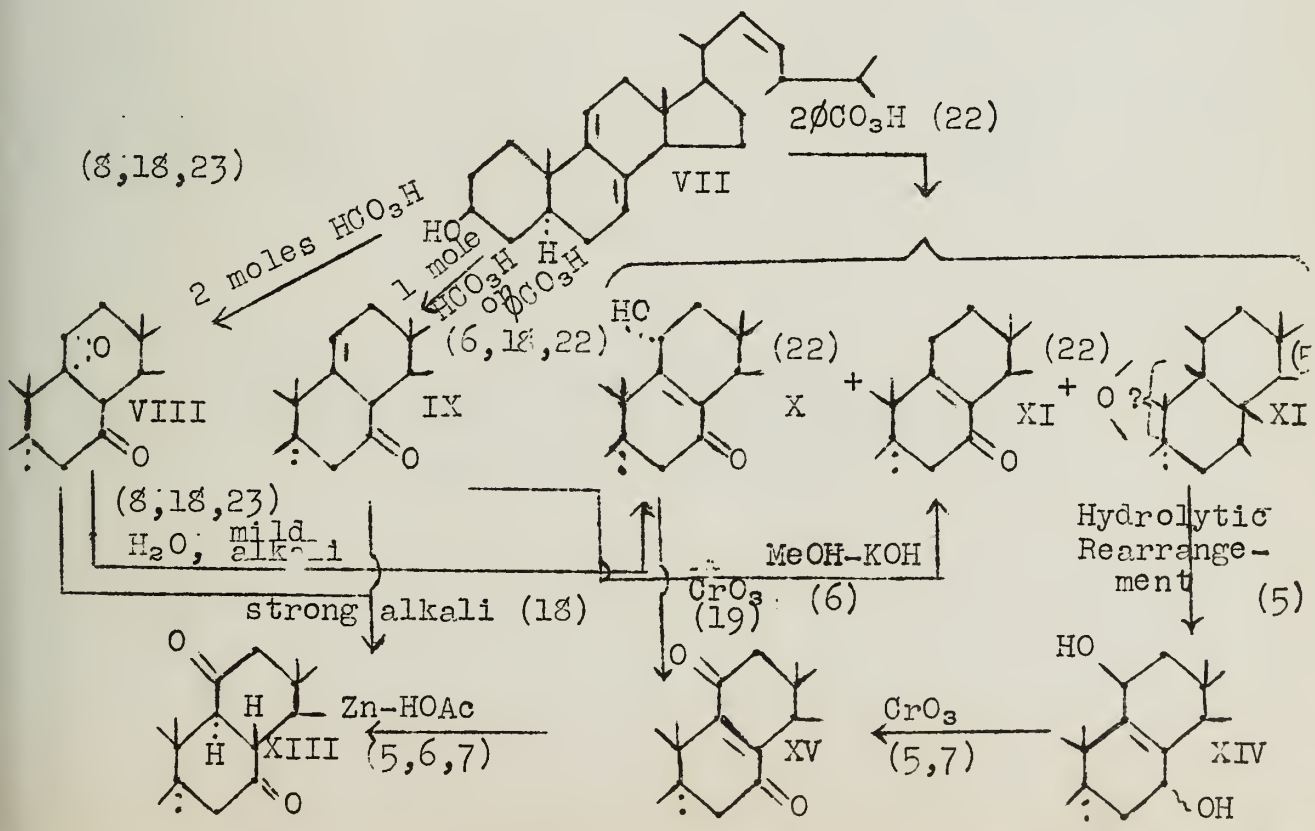


$\Delta^{9(11)}$-monolefins give the α-epoxide[4,10,21] which, upon oxidation may yield an epoxyketone[4,10] or a keto-hemiacetal[3,21], as shown with methyl $\Delta^{9(11)}$-lithocholenate acetate (V_a)[21] and methyl $\Delta^{9(11)}$-lithocholenate (V_b)[10] (R=-CH(CH_3)$CH_2CH_2COOCH_3$):



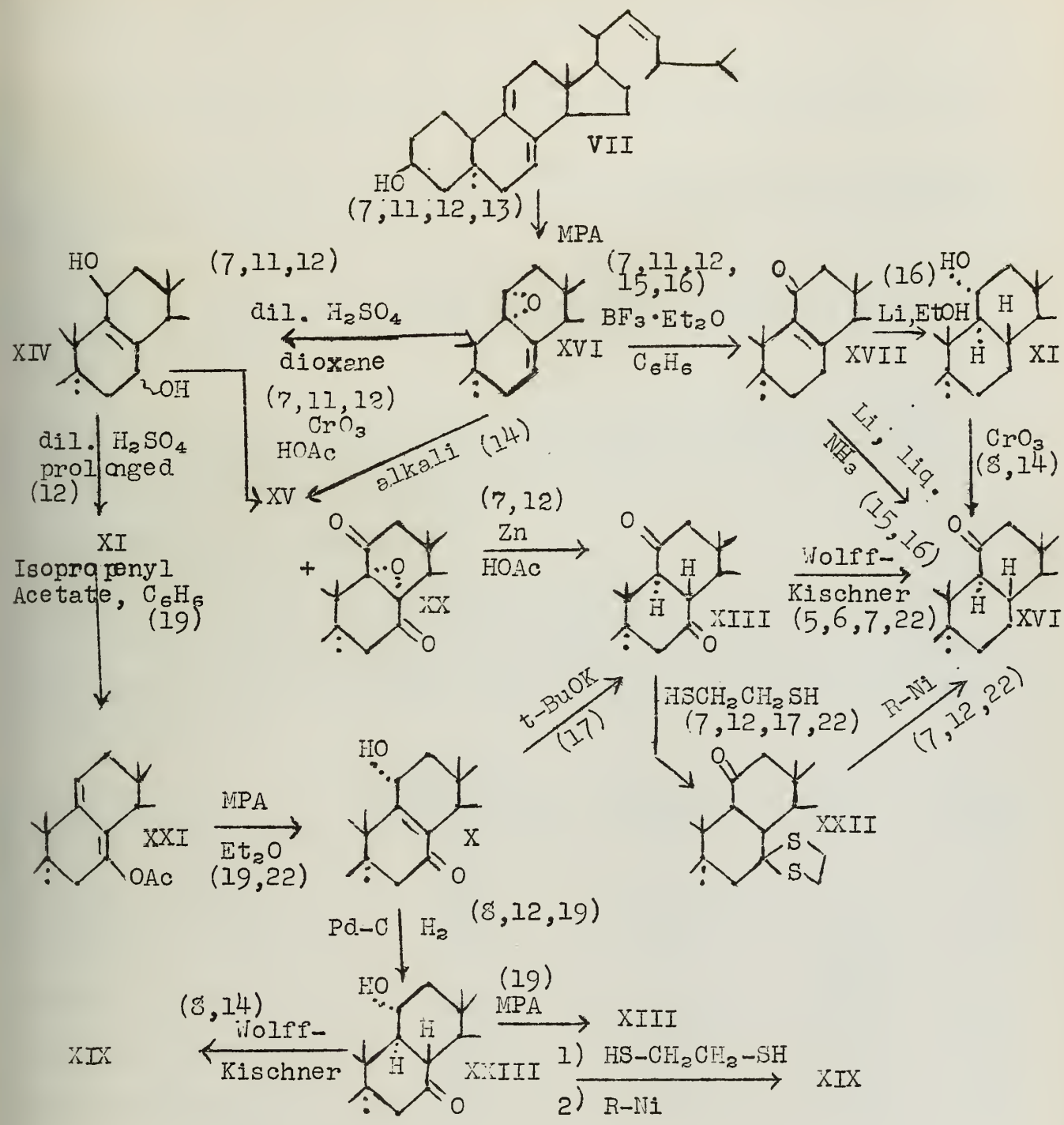
Figures I and II describe, respectively the reactions of $\Delta^{9(11)}$-dienes with performic and perbenzoic, and with monoperphthalic (MPA) acids. Not all of the reactions have been shown to to occur with the model compound-- $\Delta^{7,9(11),22}$-ergostatriene (VII) but all have been demonstrated on one or more compounds from the sterol, bile acid, or steroidal sapogenin series. The reactions cannot always be transferred from one class to another, e.g. with performic acid VII yields epoxyketones of the type VIII from sterol and steroidal sapogenins[8], but unsaturated ketones of the type XI from members of the bile-acid series[9]. References to some work in which these types of reactions have been used are given in parentheses near the appropriate arrows.

Figure I



Further transformations of VII,X,XI, and XIII are shown in Fig. II.

Figure II


VII
HO
(7,11,12,13)
MPA
HO
(7,11,12)
XIV
OH
dil. H_2SO_4
dioxane
(7,11,12)
CrO_3
HOAc
XVI
(7,11,12, 15,16)
$BF_3 \cdot Et_2O$
C_6H_6
XVII
(16)
Li,EtOH
XI
dil. H_2SO_4
prolonged
(12)
XV
alkali (14)
Li, liq. NH_3
(15,16)
CrO_3
(8,14)
XI
Isopropenyl
Acetate, C_6H_6
(19)
XX
(7,12)
Zn
HOAc
XIII
Wolff-
Kischner
(5,6,7,22)
XVI
t-BuOK
(17)
$HSCH_2CH_2SH$
(7,12,17,22)
R-Ni
(7,12,22)
XXI
OAc
MPA
Et_2O
(19,22)
X
XXII
Pd-C
H_2
(8,12,19)
(19)
MPA
XIII
(8,14)
Wolff-
Kischner
XIX
XXIII
1) $HS-CH_2CH_2-SH$
2) R-Ni
XIX

C. NBS- t-BuOH[9,24]. A $\Delta^{7,9(11)}$-diene such as methyl 3α-acetoxy- $\Delta^{7\ 9(11)}$,-choladienate yields up to three products of types IX, X, and XVII, depending on conditions; this particular reaction was run in t-BuOH with dil. H_2SO_4 at 0°.

D. $KMnO_4$-HOAc[20,22]. When treated with 5% $KMnO_4$ in HOAc at 10°, Va gives the β-epoxide, as contrasted to the α-product from the action of perbenzoic acid.

E. $Na_2Cr_2O_7 \cdot 2H_2O$ - gl.HOAc[6,22,23]. Oxidation of such dienes as methyl 3α- acetoxy- $\Delta^{7\ 9(11)}$,-choladienate can give at least two products of the types IX and XV.

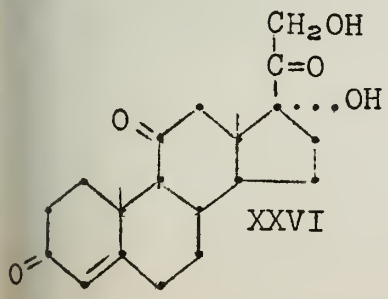
F. Fe^{++} - H_2O_2[22,23]. From $\Delta^{7,9(11)}$-cholestadiene benzoate (XXIV) the 9α,11α-oxido-7-ketone is formed[23], while from methyl 3α-hydroxy- $\Delta^{7\ 9(11)}$,-choladienate (XXV) the $\Delta^{9(11)}$- and Δ^{8}-7-ketones are formed[22].

It is of interest to note that while reductions of 11-keto steroids with $LiAlH_4$, $LiBH_4$, $NaBH_4$, or catalytic hydrogenation yield the 11β-hydroxy product, reduction with Na and boiling propanol give the 11α-hydroxy isomer[13].

Microbiological 11-Oxidation[30-9].

Only recently have processes been reported for 11-oxygenation of steroids by various microorganisms, namely: 1) Aspergillus niger, 2) Streptomyces fradiae, 3) Rhizopus nigricans, 4) Rhizopus arrhizus. The method is characterized by its simplicity, ease of workup, speed, and good yields. Some of the transformations which have been made are:

Compound Treated	Hydroxyl Introduced	Fungus	Yield	Ref.
Progesterone	11α; 11α,6	A. niger	—	30
Reichstein's Cpd. S	11α	"	—	30
Desoxycorticosterone	11α	"	—	30
Reichstein's Cpd. S	11β	S. fradiae	—	33
Desoxycorticosterone	11α	R. nig.	50-60%	35
Progesterone	11α	R. nig.	nearly quant.	35
Reichstein's Cpd. S	11α	R. nig.	60-80%	36
	6β	R. arrh.	good	36
17α-Hydroxyprogesterone	11α	R. nig.	70-75%	37
	6β	R. arrh.	45%	37
6-Dehydroprogesterone	11α	R. nig.	50-60%	38



XXVI

The greatest stimulus to this work has been the desire for better routes to cortisone (XXVI), and several articles record the use of these methods to supply new routes to the compound[25-9,36].

BIBLIOGRAPHY

1) H. Reich and T. Reichstein, Helv. Chim. Acta, 26, 562-85 (1943).
2) E. Berner and T. Reichstein, ibid., 29, 1374-81 (1946).
3) L. F. Fieser, H. Heymann and S. Rajagopalan, J. Am. Chem. Soc., 72, 2306 (1950).
4) L. F. Fieser and S. Rajagopalan, ibid., 73, 118-22 (1951).
5) E. M. Chamberlin, et al., ibid., 73, 2396-7 (1951).
6) L. F. Fieser, J. E. Herz and W. Y. Huang, ibid., 73, 2397 (1951).
7) H. Heumann, et al., Helv. Chim. Acta, 34, 2106-32 (1951).
8) G. Stork, et al., J. Am. Chem. Soc., 73, 3546-7 (1951).
9) L. F. Fieser, et al., ibid., 73, 4053-4 (1951).
10) H. Heymann and L. F. Fieser, ibid., 73, 5252-65 (1951).
11) H. Heusser, et al., Helv. Chim. Acta, 35, 295-307 (1952).
12) H. Heusser, et al., ibid., 35, 936-50 (1952).
13) H. Heusser, R. Anliker and O. Jeger, ibid., 35, 1537-41 (1952).
14) C. Djerassi, et al., J. Am. Chem. Soc., 74, 1712-15 (1952).
15) E. Schoenewaldt, et al., ibid., 74, 2696 (1952).
16) F. Sondheimer, et al., ibid., 74, 2696-7 (1952).
17) J. Romo, et al., ibid., 74, 2918-20 (1952).
18) R. Budziarek, et al., J. Chem. Soc., 1952, 2892-2900.
19) C. Djerassi, et al., J. Am. Chem. Soc., 74, 3321-3 (1952).
20) J. M. Constantin and L. H. Sarett, ibid., 74, 3908-10 (1952).
21) H. Heymann and L. F. Fieser, ibid., 74, 5938-41 (1952).
22) L. F. Fieser, W. Y. Huang and J. C. Babcock, ibid., 75, 116-21 (1953).
23) L. F. Fieser and J. E. Herz, ibid., 75, 121-4 (1953).
24) L. F. Fieser, W. P. Schneider and W. Y. Huang, ibid., 75, 124-7 (1953).
25) H. Heymann and L. F. Fieser, ibid., 73, 4054-5 (1951).
26) J. M. Chemerda, et al., ibid., 73, 4052-3 (1951).
27) G. Rosenkranz, J. Pataki and C. Djerassi, ibid., 73, 4055-6 (1951)
28) R. B. Woodward, F. Sondheimer and D. Taub, ibid., 73, 4057 (1951).
29) O. Mancera, et al., ibid., 74, 3711-12 (1952).
30) J. Fried, et al., ibid., 74, 3962-3 (1952).
31) D. H. Peterson, et al., ibid., 74, 5933-6 (1952).
32) D. H. Peterson and H. C. Murray, ibid., 74, 1871-2 (1952).
33) D. R. Golingsworth, M. P. Brunner and W. J. Haines, ibid., 74, 2381-2 (1952).
34) P. D. Meister, et al., ibid., 75, 55-7 (1953).
35) S. H. Eppstein, et al., ibid., 75, 408-12 (1953).
36) D. H. Peterson, et al., ibid., 75, 412-15 (1953).
37) P. D. Meister, et al., ibid., 75, 416-18 (1953).
38) D. H. Peterson, et al., ibid., 75, 419-21 (1953).
39) S. H. Eppstein, et al., ibid., 75, 421-2 (1953).
40) M. Sorkin and T. Reichstein, Helv. Chim. Acta, 29, 1218 (1946).

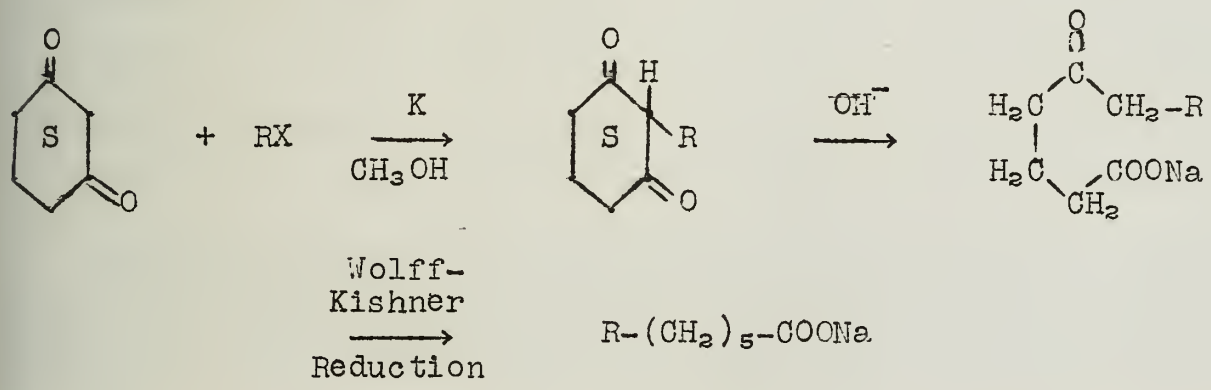
SYNTHESES OF LONG CHAIN FATTY ACIDS

Reported by John R. Demuth March 13, 1953

With the renewed interest in synthetic methods of producing long-chain fatty acids, there have been developed several new genera procedures for synthesizing them. It will be the object of this seminar to describe some of these new methods.

Stetter and Dierichs have developed a method of producing fatty acids which uses as starting material 1,3-cyclohexanedione, produced by the hydrogenation of resorcinol over Raney Nickel.[12] The success of this method depends upon the occurrence of carbon-alkylation of the dione. According to the investigations of G. Schwarzenbach,[11] 1,1-dimethyl-3,5-cyclohexanedione exists in the enol form in aqueous solution to the extent of 95.3 per cent. It seems likely that a similar equilibrium, lying much in favor of the enol form also would exist for dihydroresorcinol. Therefore, it is not surprising that until the appearance of the current series of papers by Stetter and Dierichs, only two reports of C-alkylation of this compound were to be found in the literature.[8,9]

An outline of the synthesis developed by Stetter and Dierichs is shown below.



In order to find the optimal conditions for carbon-alkylation of 1,3-cyclohexanedione, the conditions of alkylation were varied systematically. Because of its intermediate position between the lower halides which would be expected to be more reactive, and the higher alkyl halides, the reaction of which would be more interesting, n-butyl bromide was chosen as the halide for these experiments.

The reaction was studied with respect to its dependence upon solvent, the alkali metal used, concentration of 1,3-cyclohexanedion and type of alkyl halide employed.

The ratio of C- to O-alkylation was found to be independent of the alcohol chosen as solvent, although the use of methanol for this purpose led to a significant increase in over-all yield of alkylated product. Of the three alkali metals employed; lithium,

sodium, and potassium, the last named was found to give the highest C- to O-alkylation ratio. With methanol as solvent, it was found that the more concentrated the dione, the more favorable was the C/O alkylation ratio. When n-butyl iodide was used in place of the corresponding bromide, the percentage of C-alkylated product increased.

Under the conditions described above, a series of alkylated 1,3-cyclohexanediones was prepared. The results of these reactions are summarized in Table I.

Table I

Reaction of 1,3-Cyclohexanedione with Various Alkyl Iodides

Alkyl Iodide	Reaction Time	C-comp. %	O-comp. %	Total %	C/O Ratio
Methyl	45 min.	51.5	-	51.5	-
Ethyl	3 hrs.	27.2	43.0	70.2	1:1.6
n-Propyl	3 hrs.	26.0	32.5	58.5	1:1.25
n-Butyl	3 hrs.	28.4	36.1	64.8	1:1.3
n-Cetyl	24 hrs.	27.0	51.0	78.0	1:1.9

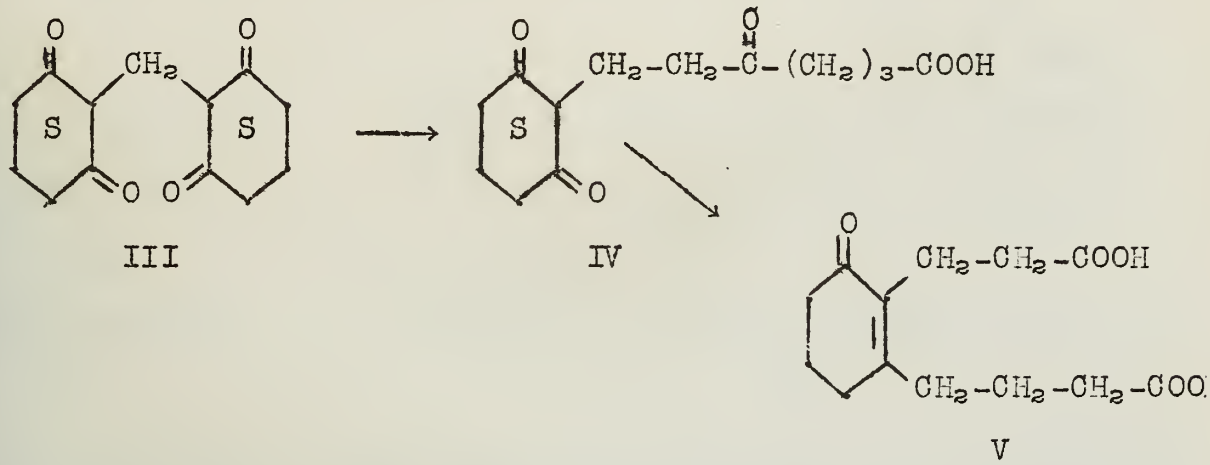
From this table, it can be seen that the size of the alkyl iodide employed has little effect on the amount of C-alkylated product obtainable or upon the ratio of C- to O-alkylation product, except that when methyl iodide was used, none of the enol ether was formed.

The carbon substituted 1,3-cyclohexanediones are colorless crystalline compounds which must be used soon after preparation for they show signs of decomposition - discoloration and development of a disagreeable odor - after a day or two. The rate of decomposition increases with increasing length of the alkyl radical introduced.

Hydrolysis of the alkylated dihydroresorcinol with baryta water yielded the 5-ketoacid which was easily converted to the saturated acid by the Huang-Minlon modification of the Wolff-Kishner reduction

In subsequent experiments directed toward extending the usefulness of this reaction, Stetter and Dierichs condensed two moles of the diketone with one mole of formaldehyde to obtain the compound shown as (III) below.[13] Under very mild conditions, (III) was converted to the expected monocarboxylic acid (IV). However, opening

of the second ring was accompanied by immediate recyclization by the loss of a molecule of water to give rise to compound (V).



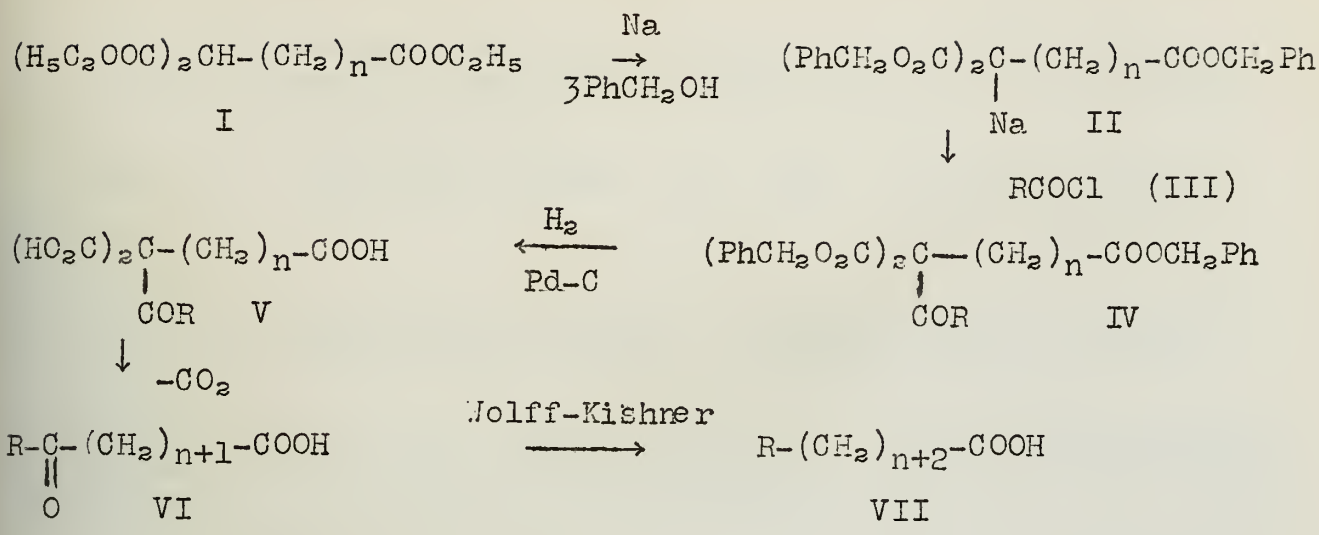
An ingenious though simple method for avoiding this difficulty was devised. By carrying out the ring opening with base in the presence of hydrazine under the conditions of the Wolff-Kishner reduction, not only was the desired 1,11-undecanedicarboxylic acid obtained in quantitative amounts, but also one step of the already short synthetic route was eliminated. Further experiments have shown that this shortened procedure is generally applicable to alkylated 1,3-cyclohexanediones.

Compounds having an active halogen were found to alkylate dihydroresorcinol rather readily. By working in aqueous rather than in methanolic solution, and using the simplified method of ring opening and reduction, relatively high yields, 65-80%, of the acids derived from alkylation of dihydroresorcinol by the following compounds were obtained: bromoacetic acid, allyl bromide, 1-bromo-2-cyclohexene, benzyl chloride (in the presence of KI) and 1,4-dibromo-2-butene (reacted with 2-moles of 1,3-cyclohexanedione).

Work is now in progress to see if the production of branched chain fatty acids is feasible by the replacement of the second active hydrogen of a 1-alkyl-2,6-cyclohexanedione by another alkyl group.[14] At the present time, one such acid, 6-methyl-7-phenyl-heptanoic acid, has been prepared.

The second synthetic route to be described is much more elaborate than the previous one, but it seems to be rather versatile and to be applicable to the production of very long chains.[4]

An outline of the method is shown below.



The advantages of this debenzylation synthesis are said to be several. First, the yields are usually 70% or higher; secondly, the "chain extender" is a malonic ester which may be obtained in several ways and; thirdly, the intermediate reactant (IV) is rendered soluble by three benzyl groups so that subsequent reaction can be carried out in not too dilute solution.

This method has been applied to the synthesis of straight chain acids containing 14, 18, 23, 38, and 56 carbons.

Ames and Bowman[2,5] have shown that long-chain unsaturated acids may be synthesized by condensing (II) with an α-alkoxy acid chloride followed by debenzylation, reduction to the glycol by use of aluminum iso-propoxide, conversion to the dibromide, and final introduction of the double bond by the use of zinc in ethanol.

By a suitable choice of starting materials and using the route outlined above, the authors were able to synthesize 9-methyloctadec-9-enoic acid, the 12-methyl and the 5,7,13,17-tetramethyl analogues of the same acid.[3]

The third method of producing long-chain fatty acids is not a new one, but is simply a modification of the well-known Kolbe electrolysis. In the ordinary Kolbe electrolysis, the salt of an acid is electrolyzed to produce the hydrocarbon formed by coupling two hydrocarbon radicals.

$$2RCOO^- \xrightarrow{e^-} R\text{-}R + 2CO_2$$

By using the half ester of a dicarboxylic acid, the ester of another dibasic acid having 2n-2 carbons is formed.

$$2KOOC\text{-}(CH_2)_n\text{-}COOC_2H_5 \xrightarrow{e^-} H_5C_2OOC\text{-}(CH_2)_n\text{—}(CH_2)_n\text{-}COOC_2H_5$$

In the procedure advocated by Greaves et al.[7,10] a mixture of a saturated carboxylic acid with the half ester of an α,ω-dicarboxylic acid is electrolyzed.

$$\underset{\text{I}}{RCOOH} + HOOC\text{-}(CH_2)_n\text{-}COOMe \rightarrow R\text{-}R + \underset{\text{II}}{R\text{-}(CH_2)_n\text{-}COOMe}$$

$$+ MeOOC\text{-}(CH_2)_{2n}\text{-}COOMe + CH_2{=}CH\text{-}(CH_2)_{n-2}\text{-}COOMe$$

To be sure, all the expected products of such an electrolysis are formed, but the use of absolute methanol as solvent and a high concentration of (I) favors the formation of (II).

A wide difference between the sizes of the coupling units can be tolerated. Stearic acid has been made by coupling a C_5 to a C_{13}, a C_9 to a C_9, and a C_{17} to a C_1 residue. Therefore by a careful choice of reactants, a product is formed which is uncontaminated by substances of the same or very similar molecular weight, so isolation of the desired compound in a pure state is simplified.

BIBLIOGRAPHY

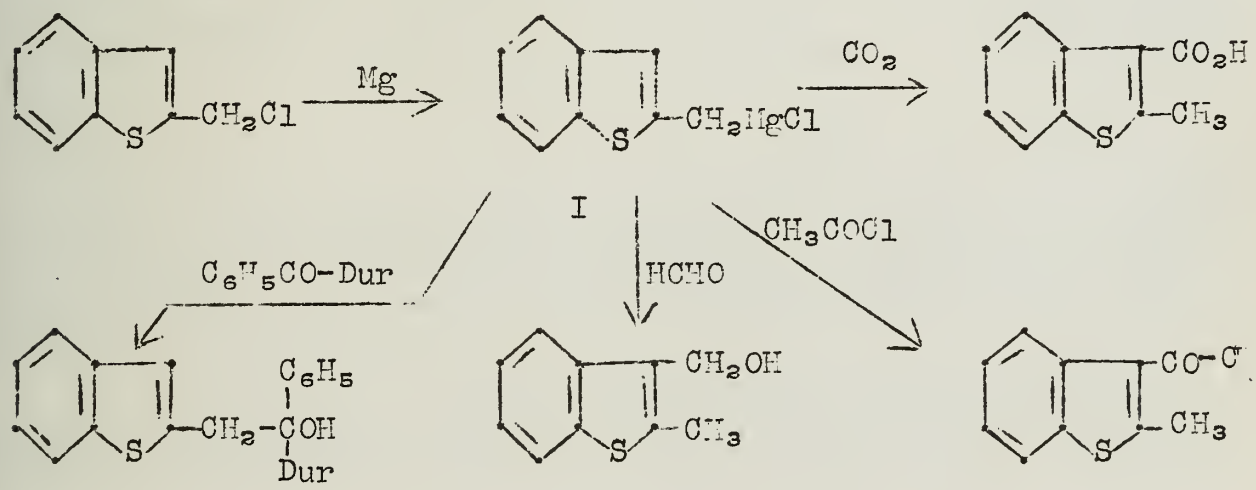
1. Ames, D. E., Bowman, R. E. and Mason, R. G., J. Chem. Soc., 1950, 174.
2. Ames, D. E. and Bowman, R. E., ibid., 1951, 1079.
3. Ames, D. E. and Bowman, R. E., ibid., 1951, 1087.
4. Ames, D. E. and Bowman, R. E., ibid., 1952, 677.
5. Bowman, R. E., ibid., 1952, 177.
6. Bowman, R. E. and Mason, R. G., ibid., 1951, 2748.
7. Greaves, J. S., Linstead, R. P., Shephard, B. R., Thomas, S. L. S. and Weedon, B. C. L., ibid., 1950, 3326.
8. Howett, C. L., ibid., 1936, 50.
9. Klingenfuss, M., Festschrift Emil Barell, Basel, 1936, 217.
10. Linstead, R. P., Lunt, J. C., and Weedon, B. C. L., J. Chem. Soc. 1950, 3331.
11. Schwarzenbach, G., Helv. Chim. Acta. 27, 1059 (1944).
12. Stetter, H. and Dierichs, W., Chem. Ber., 85, 61 (1952).
13. Stetter, H. and Dierichs, W., ibid., 85, 290 (1952).
14. Stetter, H. and Dierichs, W., ibid., 85, 1061 (1952).

ABNORMAL REACTIONS OF HETEROCYCLIC GRIGNARD REAGENTS

Reported by G. W. Parshall March 15, 1953

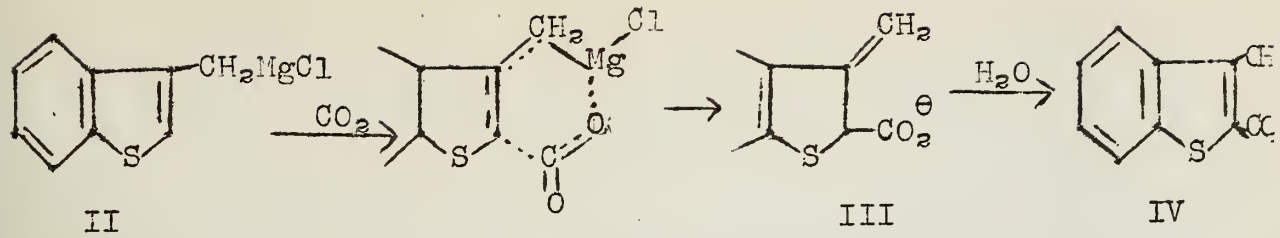
Since the development of the "cyclic reactor" which facilitates the preparation of Grignard reagents from extremely reactive alkyl halides,[1] the preparation of several heterocyclic analogues of benzylmagnesium chloride has been reported. In their reactions with carbonyl compounds, these new Grignard reagents have been found to undergo allylic rearrangements similar to these which have been observed in the benzyl series.[2] These "abnormal" reactions have acquired particular significance since it was observed that the extent of rearrangement is dependent of the aromaticity of the system being studied.[3,4]

Grignard Reagents with the Thiophene Nucleus--- Both 2- and 3-(chloromethyl)-thianaphthene yield stable Grignard reagents in the cyclic reactor, but when these are allowed to react with carbonyl compounds, the products are predominantly abnormal.[4,5] The reactions of 2-thianaphthenylmethylmagnesium chloride (I) with carbon dioxide, acetyl chloride, formaldehyde and benzoyldurene are shown below.

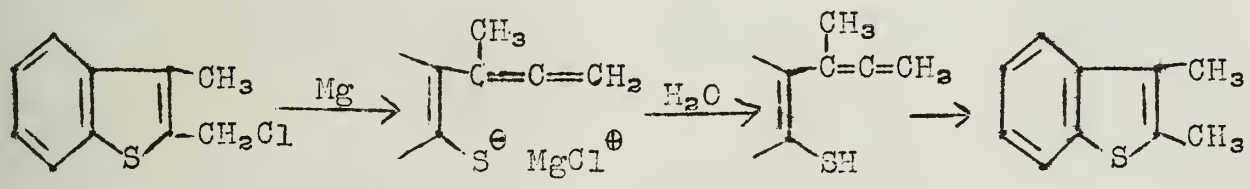


3-Thianaphthenylmethylmagnesium chloride (II) behaves similarly in that rearranged products are obtained from its reactions with ethyl chlorocarbonate and formaldehyde and the unrearranged product is obtained with benzoyldurene. However it differs in that a mixture of acids is obtained when it is carbonated. The ratio of the rearrangement product (3-methyl-2-thianaphthenoic acid) to the normal product (3-thianaphthenylacetic acid) is 3.5 to 1.

One mechanism which has been postulated for this type of rearrangement[6] is illustrated in the carbonation of 3-thianaphthenylmethylmagnesium chloride (II).



In an attempt to isolate an "isoaromatic" product corresponding to the intermediate (III), Gaertner treated 2-chloromethyl-3-methylthianaphthene (V) with magnesium in the cyclic reactor and carbonated the resulting solution. However only a trace of an organic acid could be isolated from the reaction mixture. The main product was 2,3-dimethylthianaphthene (VII) which apparently resulted from a cleavage reaction similar to that previously observed with 2-(chloromethyl)-benzofuran.[7] The intermediate o-(α-methylallenyl)-thiophenol (VI) could not be isolated but the corresponding thiolacetate was obtained by treating the reaction mixture with acetyl chloride.[8]

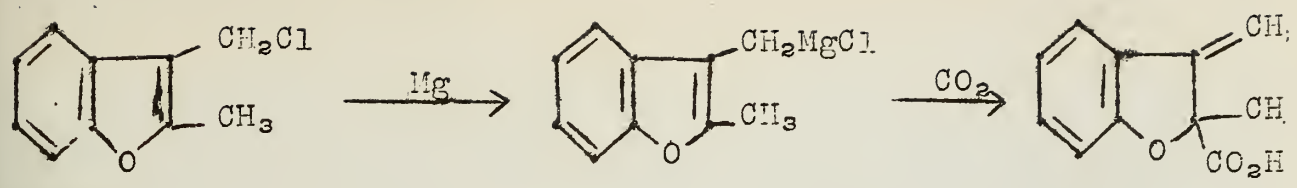


The reactions of 2-thenylmagnesium chloride are very similar to those of 2-thianaphthenylmethylmagnesium chloride (I) except that a mixture of normal and rearranged acids is obtained when it is carbonated. The normal product, 2-thienylacetic acid, predominates in the mixture.[9]

When the Grignard reagent prepared from 5-methyl-2-thenyl bromide is carbonated, only the rearranged product, 2,5-dimethyl-3-thenoic acid, is obtained.[10]

<u>Grignard Reagents with the Furan Nucleus</u>---To date, no one has succeeded in preparing a Grignard reagent from an α-furfuryl halide since these β-halo ethers undergo cleavage when they are treated with magnesium.[7,11] In contrast 3-furfuryl chloride forms a Grignard reagent in 71% yield by conventional methods. When 3-furfurylmagnesium chloride is carbonated, a mixture of 3-furylacetic acid and 3-methyl-2-furoic acid is produced. The latter, the rearranged product, constitutes approximately 90% of the mixture.[3]

An "isoaromatic" product is obtained when the Grignard reagent prepared from 3-chloromethyl-2-methylbenzofuran (VIII) is treated with ethyl chlorocarbonate. This product, 2-methyl-3-methylene-2,3-dihydro-2-benzofuroic acid (IX), is also obtained when the Grignard reagent is carbonated, but carbonation yields in addition a trace of the normal product, 2-methyl-3-benzofurylacetic acid.[12]



VIII IX

Relationship to Aromatic Character---It has been observed that aromatic systems possessing high resonance energies have little tnedency to undergo the type of rearrangement described in this paper. This tendency has been quantitatively expressed in terms of the proportion of "abnormal" acid produced upon carbonation of the Grignard reagent. The table below indicates the possible relationship involved. The α-picolyl Grignard reagent is placed above benzylmagnesium chloride because the latter undergoes rearrangement in its reaction with acetyl chloride while the former does not.[13]

Grignard Reagent	Proportion of abnormal acid	Resonance energy
α-Picolyl	0 %	43 kcal./mol
Benzyl	0	39
2-Thenyl	33	31
3-Thianaphthenylmethyl	78	--
3-Furfuryl	90	23
2-Thianaphthenylmethyl	100	--

BIBLIOGRAPHY

1. D. C. Rowlands, K. W. Greenlee and C. E. Boord, Abstracts, 117th A. C. S. Meeting, Philadelphia, Pa., p. 8L (April 1950).
2. R. O. Kerr, Org. Seminar, Univ. of Illinois (Nov. 2, 1951).
3. E. Sherman and E. D. Amstsutz, J. Am. Chem. Soc., 72, 2195 (1950).
4. R. Gaertner, ibid., 74, 2185 (1952).
5. R. Gaertner, ibid., 74, 766 (1952).
6. J. R. Johnson, ibid., 55, 3029 (1933).
7. R. Gaertner, ibid., 73, 4400 (1951).
8. R. Gaertner, ibid., 74, 2991 (1952).
9. R. Gaertner, ibid., 73, 3934 (1951).
10. J. Lecocq and N. P. Buu Hoi, Compt. rend., 224, 658 (1947).
11. H. Normant, Bul. soc. chim. France, (5) 12, 609 (1945).
12. R. Gaertner, J. Am. Chem. Soc., 74, 5319 (1952).
13. H. Gilman and J. L. Towle, Rec. trav. chim., 69, 428 (1950).

THE WILLGERODT REACTION

Reported by S. L. Jacobs March 20, 1953

A reaction (I, see below) in which a ketone may be transformed into an amide with the same number of carbon atoms was first described by Willgerodt in 1887.[1] The reagent generally used for this purpose is ammonium polysulfide, prepared by saturating concentrated aqueous ammonia with hydrogen sulfide and dissolving in the solution 10% by weight of sulfur. A modification (II) of the reaction was discussed by Kindler in 1941[2] which involved substitution of a mixture of a dry amine and sulfur for the aqueous $(NH_4)_2S_x$ to obtain thioamides. A further and widely used modification of Kindler's procedure was developed by Schwenk and Bloch[3] who utilized morpholine as the amine. The Willgerodt and Kindler reactions have been extended to the aryl-substituted acetylenes and olefins to yield carbonamides and thioamides (III).[4]

$$\text{(I)}\quad \phi CO(CH_2)_nCH_3 \xrightarrow[H_2O]{(NH_4)_2S_x} \phi CH_2(CH_2)_nCONH_2$$

$$\text{(II)}\quad \phi CO(CH_2)_nCH_3 \xrightarrow{HNR_2,\ S} \phi CH_2(CH_2)_nCSNR_2$$

$$\text{(III)}\quad \phi CH{:}CHCH_3 \begin{cases} \xrightarrow{\text{Willgerodt}} \phi CH_2CH_2CONH_2 \\ \xrightarrow{\text{Kindler}} \phi CH_2CH_2CSNR_2 \end{cases}$$

Addition of pyridine[4] or dioxane[5] as solvent allows the reaction to proceed at a lower temperature so that side reactions are minimized.

Several reviews of the Willgerodt reaction are available which cover the literature up to 1948.[6,7,8] This seminar will review some of this work and summarize that which has been done since.

The reaction applies both to aryl-alkyl ketones and to completely aliphatic ketones where there is a tendency to preferentially produce the amide group at the end of the shorter chain.[9]

$$CH_3CH_2CH_2COC^{14}H_3 \xrightarrow[H_2O]{(NH_4)_2S_x} C^{14}H_3(CH_2)_3CONH_2 + CH_3(CH_2)_3C^{14}ONH_2$$

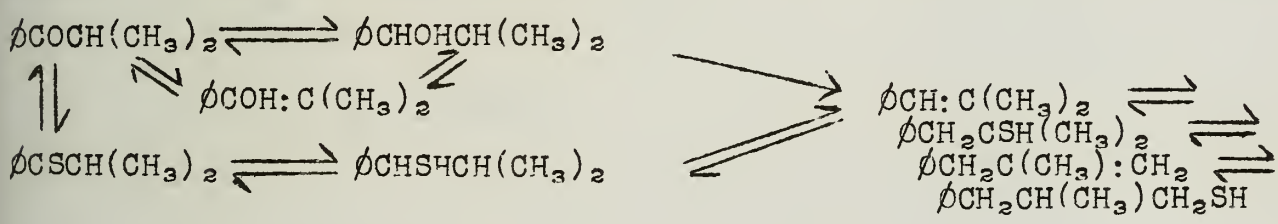
Total yield = 30% (32%) (68%)

It has been observed that in the case of certain ketones, the yield drops drastically with reaction temperatures above 160°C. This has been shown in some cases to be due to instability of the product (e.g. 2-thienylacetamide).[10]

It is currently the opinion of all workers that these reactions, whether Willgerodt or Kindler, and whether starting with ketones, olefins, acetylenes, or even alcohols, halides, amines or thiols, all proceed according to the same mechanism involving the preliminary formation of a labile intermediate with an unsaturated C-C bond in the chain.[4,11,12,13,14] In the case of ketones, this linkage is pictured as originally being located adjacent to the carbonyl group of the ketone through enolization of the alpha-hydrogen. A shift of this bond towards the terminal carbon occurs

through successive additions and eliminations of an unsymmetrical reagent. According to Carmack, et al., the intermediate is acetylenic; this cannot be considered likely since branched-chain compounds as $\phi COCH_2CH(CH_3)_2$ are known to give the expected amide, $\phi CH_2CH_2CH(CH_3)CONH_2$, with no loss of carbon. Also, $\phi COCH_2CD_2CH_2CH_3$ has been shown to retain some of its deuterium after having undergone the reaction.[11] All the deuterium would have been lost were the intermediate acetylenic. It may be noted here that the reaction will not proceed with a chain containing a quaternary carbon atom. McMillan and King,[13,14] however, are of the opinion that the intermediate is olefinic. They believe that hydrogen sulfide is the specific unsymmetrical reagent that causes migration of the olefinic bond to a terminal position and finally the formation of a primary thiol which is irreversibly oxidized by sulfur (the amine is also involved here) to the thioamide which remains as such in the Kindler modification or is converted to the carbonamide in the reactions which are run in aqueous media. Some retention of deuterium by the ketone $\phi COCH_2CD_2CH_2CH_3$ is found as would be expected from an olefinic intermediate. It has further been shown that there is no rearrangement of the carbon skeleton during the Willgerodt reaction,[12] contrary to results previously reported.[15]

The reaction might best be described according to the following scheme in the light of the information available to date:



Then, if R = $\phi CH_2CH(CH_3)$-, as in the example above --

$$2\ RCH_2SH + S \longrightarrow RCH_2SSCH_2R + H_2S \quad \text{(well established)}$$
$$R'_2NH + S \longrightarrow R'_2NH \cdot S \longrightarrow R'_2NSH \quad (R'_2NH = \text{Morpholine})$$

Both the amine and the sulfur are necessary for the next step --

$$R'_2NSH + RCH_2SSCH_2R \rightleftharpoons RCH(NR'_2)SSCH_2R + H_2S$$

$$RCH(NR')SSCH_2R + R'_2NSH \longrightarrow H_2S + RCH(NR'_2)SSCHR(NR'_2) \xrightarrow{2\ R'_2NH} 2\ RCH(NR'_2)_2 + H_2S + S$$

$$RCH(NR'_2)_2 + S \longrightarrow RCSNR'_2 + HNR'_2$$

The overall equation for this irreversible oxidation would be:

$$RCH_2SH + R'_2NH + 2\ S \longrightarrow RCSNR'_2 + 2\ H_2S$$

It has been shown that compounds other than ketones, olefins, and acetylenes will give the predicted product in the Willgerodt Reaction. In the following table, the indicated yields of phenylacetamide were obtained using yellow ammonium polysulfide in dioxane in sealed tubes at 170°C. for seven hours.[16]

1-Phenylethylamine	61%	2-Phenylethylamine	32%
1-Phenylethyldimethylamine	31	1-Phenylethyl bromide	40
1-Phenylethyl-(monoethanol)-amine	63	2-Phenylethyl bromide	66
1-Phenylethyl-(diethanol)-amine	66	Styrene oxide	87
Phenacylpyridinium iodide	53	β-Bromostyrene	80
ω-Morpholinoacetophenone	72		

These compounds are all very similar to postulated intermediates o either Carmack or McMillan and King, or they may very easily be converted to these intermediates.

The Willgerodt reaction has been applied to a series of mercaptans, primary and secondary alcohols.[17] The following table illustrates the results obtained using five parts by weight of aqueous ammonium polysulfide solution at 210°C. for 5-16 hours.

Starting Material	Yield	Product
EtSH		$AcNH_2$
PrSH		$EtCONH_2$
BuSH		$PrCONH_2$
$C_8H_{17}SH$		caprylamide
$C_{10}H_{21}SH$	100%	capramide
$C_6H_5CH_2SH$	53	$C_6H_5CONH_2$
$C_6H_5CH_2CH_2SH$	95	$C_6H_5CH_2CONH_2$
Me_2CHCH_2SH		$Me_2CHCONH_2$
Me_2CHSH or $CH_2{:}CHCH_2SH$		$EtCONH_2$
$C_6H_5CH(CH_3)SH$	44	$C_6H_5CH_2CONH_2$
Me_2CHSH		$EtCONH_2$
$CH_2{:}CHCH_2OH$	34	$EtCONH_2$
Me_3COH or Me_3CSH		$Me_2CHCONH_2$
$C_6H_5CH(CH_3)OH$	48	$C_6H_5CH_2CONH_2$
$Me_2CHCH(C_6H_5)OH$		$C_6H_5CH_2CH(Me)CONH_2$
Et_2CHOH		$BuCONH_2$

The action of 3.5 grams of sulfur and 25 grams of yellow ammonium polysulfide in 25 ml. of dioxane on 5 grams of various thiophene derivatives in sealed tubes at 150-160°C. gave the following results:[10,18,19]

Thienyl Compound	Subst'd Thienyl Amide Obtained	Yield
2,5-Me_2-3-thienyl Me Ketone	3-Thienylacetamide	95%
5-Et-2-thienyl Me ketone	2-thienylacetamide	55
5-Me-2-thienyl Me ketone	2-thienylacetamide	54
3,4-Me_2-2-thienyl Me ketone	2-thienylacetamide	30
3-Me-2-thienyl Me ketone	2-thienylacetamide	26
2,3-Me_2-5-thienyl Me ketone	5-thienylacetamide	55
3-thienyl Me ketone	3-thienylacetamide	13
2-thienyl Me ketone	2-thienylacetamide	45
2-thienyl acetone	2-thienylpropionamide	28
2-vinylthiophene	2-thienylacetamide	30
2-thienylcarboxaldehyde	2-thienylcarboxamide	70
2-thienylmethylcarbinol	2-thienylacetamide	35

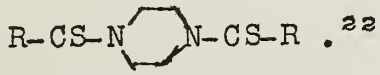
Thioamides such as $ArCH_2\overset{\overset{S}{\|}}{C}NR'_2$ (NR'_2 = morpholine) were prepared from the following ketones containing an aryl radical substituted with hydroxyl, nitro, amino, or acylamino groups:[20]

o-$(OH)C_6H_4COCH_3$	p-$(OH)C_6H_4COCH_3$
3,4-$(OH)_2C_6H_3COCH_3$	m-$(H_2N)C_6H_4COCH_3$
p-$(H_2N)C_6H_4COCH_3$	m-$(CH_3CO_2)C_6H_4COCH_3$
m-$(CH_3CONH)C_6H_4COCH_3$	o-$(CH_3CONH)C_6H_4COCH_3$
p-$(CH_3CONH)C_6H_4COCH_3$	

Some completely aliphatic ketones that have undergone the Willgerodt Reaction with $(NH_4)_2S_x$ are:

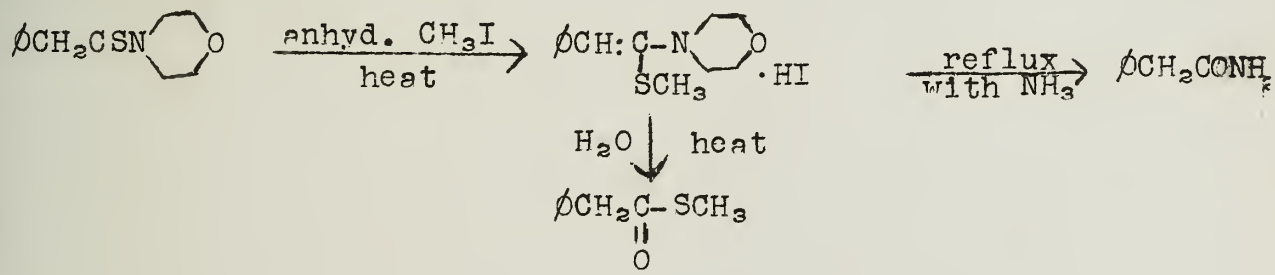
Ketone	Amide	Ref.
$CH_3CH_2COCH_3$	$CH_3CH_2CH_2CONH_2$	(9)
$CH_3CH_2CH_2COCH_3$	$CH_3CH_2CH_2CH_2CONH_2$	(9)
$C_5H_{11}COCH_3$	$CH_3(CH_2)_5CONH_2$	(9)
$(CH_3)_2CHCH_2COCH_3$	$(CH_3)_2CHCH_2CH_2CONH_2$	(21)
$CH_3CH_2COCH_2CH_3$	$CH_3(CH_2)_5CONH_2$	(21)

Piperazine and sulfur have been used for the reaction and give a product of the form



[22]

Some thioamides which are formed in the Willgerodt-Kindler reaction are unstable to acids or alkali which are used for hydrolysis to the acid. For such compounds a method has been developed for thiomorpholide breakdown without disruption of the entire molecule:[23]



BIBLIOGRAPHY

1. Willgerodt, Ber. 20, 2467 (1887); 21, 534 (1888).
2. Kindler and Li, Ber. 74, 321 (1941).
3. Schwenk and Bloch, J. Am. Chem. Soc. 64, 3051 (1942).
4. Carmack and DeTar, ibid., 68, 2025, 2029 (1946).
5. Fieser and Kilmer, ibid., 62, 1354 (1940).
6. Carmack and Spielman, "Organic Reactions" Vol. III, 1946.
7. Leubner, Organic Seminar, Nov. 8, 1946.
8. Caesar, Organic Seminar, March 18, 1949.

9. Cerwonka, Anderson and Brown, J. Am. Chem. Soc. 75, 28 (1953).
10. Blanchette and Brown, ibid., 74, 1066 (1952).
11. Cerwonka, Anderson and Brown, ibid., 75, 30 (1953).
12. Brown, Cerwonka and Anderson, ibid., 73, 3735 (1951).
13. King and McMillan, ibid., 68, 632 (1946).
14. McMillan and King, ibid., 70, 4143 (1948).
15. Dauben, Reid, Yankwich and Calvin, ibid., 72, 121 (1950).
16. Gerry and Brown, ibid., 75, 740 (1953).
17. King (to Winthrop-Stearns, Inc.) U.S. 2,459,706, Jan. 18, 1949 C.A. 43, 3028b (1949).
18. Blanchette and Brown, J. Am. Chem. Soc. 73, 2779 (1951).
19. Brown and Blanchette, ibid., 72, 3414 (1950).
20. King and McMillan (to Winthrop-Stearns Inc.) U.S. 2,568,011, Sept. 18, 1951; C.A. 46, 3081b (1952).
21. King (to Winthrop-Stearns Inc.) U.S. 2,456,785, Dec. 21, 1948; C.A. 43, 3027i (1949).
22. Chabrier and Renard, Compt. Rend. 228, 850 (1949).
23. Rogers, J. Chem. Soc. 1950, 3350.

RECENT STUDIES ON THE DECOMPOSITION OF BENZOYL PEROXIDE

Reported by James C. Kauer March 20, 1953

Benzoyl and related peroxides have been widely used as source of free radicals for the initiation of chain reactions. These peroxides have been recently studied for possible synthetic applications.

The kinetics of the thermal decomposition of benzoyl peroxide in various solvents was systematically studied in 1946.[1] It was found that the rate of decomposition of the peroxide could be represented by

$$-\left(\frac{dC}{dt}\right) = k_1 C + k_2 C^{1.5}$$

where k_1 was the first order rate constant due to the spontaneous decomposition of the peroxide, and k_2 was a higher order rate constant representing the induced decomposition of peroxide by secondary radicals.[2,3]

1) $(\phi COO)_2 \xrightarrow{k_1} 2\ \phi COO\cdot$

2) $\phi COO\cdot \longrightarrow \phi\cdot + CO_2$ RH=Solvent

3) $\phi COO\cdot + RH \longrightarrow \phi COOH + R\cdot$

These secondary radicals could attack the peroxide to initiate a chain decomposition.

4) $\phi\cdot$ (or R·) + $(\phi COO)_2 \xrightarrow{k_2} \phi COO\phi + \phi COO\cdot$

It was believed that a primary decarboxylation reaction might also take place.

5) $(\phi COO)_2 \xrightarrow{\Delta} \phi COO\phi + CO_2 + \phi\cdot$

Recent work has tended to disprove this.[4]

The Decomposition of Substituted Benzoyl Peroxides[1,2,5]

Recently kinetic studies of the decomposition of symmetrically substituted dibenzoyl peroxides have been run on dilute peroxide solutions in acetophenone. Under these conditions the induced decomposition was inhibited; the reaction was first order in peroxide.

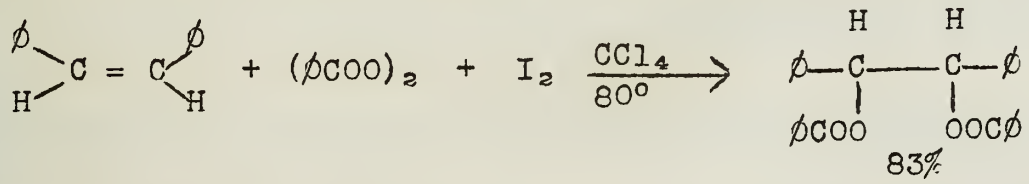
It was found that the ortho-substituted peroxides decomposed at a much higher rate than the meta- or para-substituted. This effect was probably due to the electrical repulsion of the substitutent groups.

Electron releasing groups in the meta and para positions were found to increase the rate of decomposition. This was attributed to an increase in the repulsion between the carboxyl dipoles. Electron withdrawing groups had an opposite effect, although a minimum was reached. Very strongly electronegative groups seemed

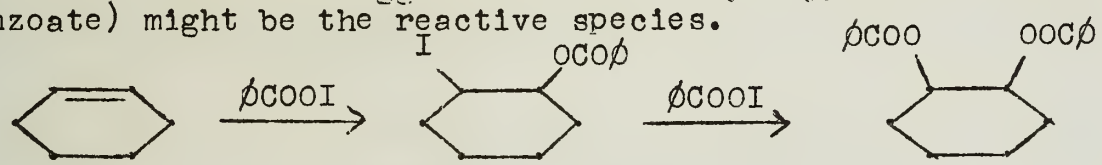
to reverse the trend. The bis-p-nitrobenzoyl peroxide, for instance, decomposes at a rate very close to that of the unsubstituted peroxide. It has been suggested that this enhanced reactivity may be due to a reversal in the dipole direction resulting in increased repulsion between the carboxyl groups.

Decomposition of Benzoyl Peroxide in the Presence of Iodine

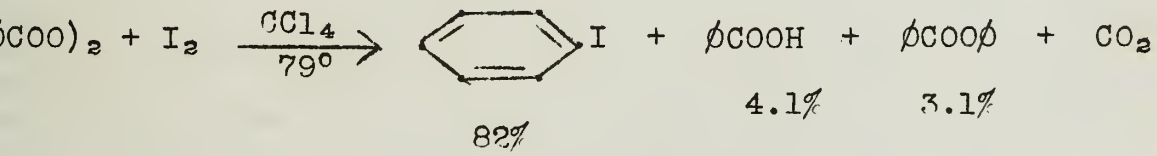
In 1945 it was reported that benzoyl peroxide reacted with olefins in the presence of iodine to form dibenzoates.[6]

6) 

With cyclohexene not only was the dibenzoate isolated but also the iodobenzoate. This latter reacted further to produce the dibenzoate. The reaction suggested that benzoyl hypoiodite (iodine (I) benzoate) might be the reactive species.

7) 

Hammond has recently observed that benzoyl peroxide will react with iodine in the presence of carbon tetrachloride to produce high yields of iodobenzene.

8) 

The iodine effectively inhibits the induced reaction by removing the initially formed radicals from solution. The reaction is first order in peroxide and independent of iodine concentration. The utilization of iodine seems to be abnormally high at first. An intermediate capable of reducing thiosulfate seems to build up in the reaction. The following mechanism is proposed:

9) $(\phi COO)_2 \longrightarrow 2\ \phi COO\cdot$

10) $\phi COO\cdot + I_2 \longrightarrow \phi COOI + I\cdot$

11) $\phi COOI \longrightarrow \phi I + CO_2$

12) $2I\cdot \longrightarrow I_2$

It is known that benzoyl hypoiodite is readily hydrolyzed by water. The following reactions were run:

15) $(\phi COO)_2 + I_2 + H_2O \xrightarrow[79^\circ]{CCl_4} \phi COOH$ (Quantitative)

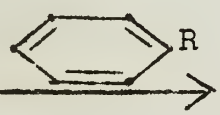
16) $(\phi COO)_2 + H_2O \xrightarrow[79^\circ]{CCl_4} \phi Cl + Cl_3CCCl_3 + CO_2$ (No Benzoic Acid)

The observed results would be expected on a basis of benzoyl hypoiodite as an intermediate. The quantitative yield of benzoic acid in reaction 15 also indicates that decarboxylation does not occur in the primary process of thermal decomposition (see reaction 5) but is strictly a secondary reaction.

When reaction 8 was run in benzene, 10% decarboxylation of the benzoate radical took place.

Decomposition of Benzoyl Peroxide in the Presence of the Triphenylmethyl Radical

In 1937 Wieland reported that dibenzoyl peroxide decomposed in the presence of triphenylmethyl.[8,9]

17) $\phi_3C\cdot + (\phi COO)_2 \longrightarrow$  ϕ_3C-  $-R + \phi_3COC(=O)-\phi + \phi COOH$

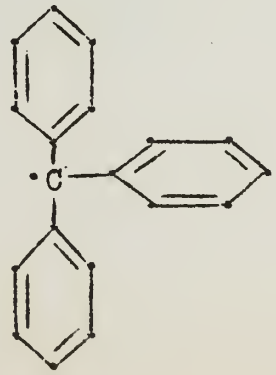
This reaction took place rapidly at room temperature. One of the aryl groups of the product tetraarylmethane was derived from the solvent. Hammond repeated this work and found that the yields of tetraphenylmethane ranged from 20% to 30% on a basis of triphenylmethyl.[10,11] Since the reaction proceeds at room temperature, it seems unlikely that the spontaneous decomposition of peroxide occurs to a significant extent. The reaction is attributed to the induced decomposition of peroxide by trityl radical.

18) $T\cdot + (\phi COO)_2 \longrightarrow \phi COOT + \phi COO\cdot$

19) $\phi COO\cdot + T\cdot \longrightarrow \phi COOT$ ArH = Aromatic Solvent

20) $\phi COO\cdot + ArH \longrightarrow \phi COOH + Ar\cdot$

21) $Ar\cdot + T\cdot \longrightarrow ArT$

T.= 

This reaction differs from other reactions in which benzoate radicals are postulated as intermediates in that no decarboxylatio seems to occur. Even when the reaction is carried out at elevated temperatures no carbon dioxide is produced. If benzoate radicals are involved in both mechanisms, the only significant difference in their environment is the nature of the other radicals in solution. If radicals influence these reactions, they must do so in concerted reactions in which two radicals attack the solvent simultaneously. One suggested explanation is that reactions 20 and 21 occur as a concerted reaction:

$$22)\quad T^{\bullet} + ArH + \phi COO^{\bullet} \longrightarrow \phi COOH + ArT$$

An argument based on a study of the ratio of ester to acid produced appears to exclude this possibility.

Another explanation has been advanced. It seems possible that when benzoate radicals are formed in pairs in the thermal decomposition reaction, these radicals may make concerted attacks on a solvent molecule while they are held in close proximity in the "solvent cage". The benzoate radicals produced by the attack of trityl radicals on peroxide are single entities, however, and in solution rarely last long enough to make a close enough approach to each other to make a concerted attack on a solvent molecule.

This may also explain the differences observed in the reactivity of certain other radicals which are apparently identical in nature but differ in the method of generation.

BIBLIOGRAPHY

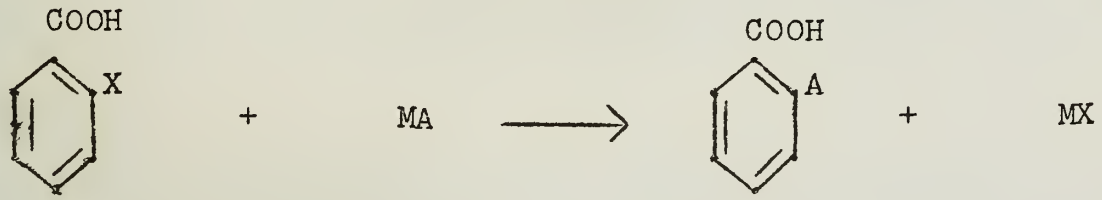
1. Nozaki and Bartlett, J. Am. Chem. Soc., 68, 1686 (1946).
2. Hartman, Sellers, and Turnbull, ibid., 69, 2416 (1947).
3. Barnett and Vaughan, J. Phys. Coll. Chem., 51, 926 (1947).
4. Hammond and Soffer, J. Am. Chem. Soc., 72, 4711 (1950).
5. Blomquist and Buselli, ibid., 73, 3883 (1951).
6. Perret and Perrot, Helv. Chim. Acta. 28, 558 (1945).
7. Hammond, J. Am. Chem. Soc. 72, 3737 (1950).
8. Wieland, Ploetz, and Indest, Ann. 532, 166 (1937).
9. Wieland and Meyer, ibid., 551, 249 (1942).
10. Hammond and Raave, J. Am. Chem. Soc. 73, 1891 (1951).
11. Hammond, Rudesill, and Modic, ibid., 73, 3929 (1951).
12. Swain, Stockmayer, and Clark, ibid., 72, 5426 (1950).

THE REACTION OF ortho-HALOBENZOIC ACIDS WITH NUCLEOPHILIC REAGENTS

Reported by Harry J. Neumiller March 20, 1953

I. HISTORICAL INTRODUCTION

The high reactivity of the halogen substituent in ortho-chlorobenzoic acid in the presence of a copper catalyst was discovered by Ullmann[6,7] in 1903. This has since been extended to include the copper catalyzed reactions of ortho-halobenzoic acids and a variety of substituted ortho-halobenzoic acids with a large number of nucleophilic reagents. The general formal reaction is given by

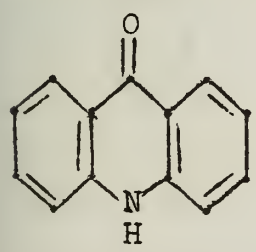
(1) 

where X in most cases is Cl, Br, (rarely I); A is -NHAr, -OAr, -NRAr, - NRH, $-NR_2$, -OR, $-NH_2$, -OH; and M is generally H, Na, K.

II. SYNTHETIC VALUE

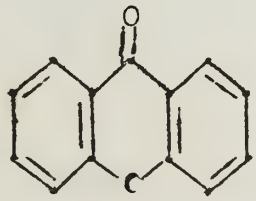
The products obtained with aryl amines can be cyclized to yield acridone derivatives (I), reduction of which gives acridine derivatives (II), or the products can be cyclized directly to acridines. Important derivatives of acridine include dyes, bactericides, and the antimalarial drug atabrine, the use of this reaction in the synthesis of atabrine[11] being perhaps its most important commercial application to date.

Cyclization of the products obtained with phenols leads to xanthone derivatives (III). Substituted anthranilic acids result from treating ortho-chlorobenzoic acid derivatives with ammonia.[12] An early method[9] for hydrolysis of substituted ortho-chlorobenzoic acids to salicylic acid derivatives by treatment under pressure with water, lime, and copper powder has experimental disadvantages.[1] This hydrolysis is now accomplished in a recently described[3] improved general procedure by treatment with aqueous K_2CO_3 in the presence of CuI and copper powder at 150-180° and 70-130 p.s.i.



Acridone
I

Acridine
II



Xanthone
III

III. CATALYST

The reaction (1) requires the presence of a metallic catalyst The most effective and generally used are metallic copper, cuprous or cupric salts, or some combination of these. Ullmann[8] found tha salts of iron, nickel, zinc, lead, and platinum (listed in order of decreasing effectiveness) would also catalyze the reaction, but not so effectively as copper or copper salts. Salts of manganese and tin were found not to catalyze the reaction.

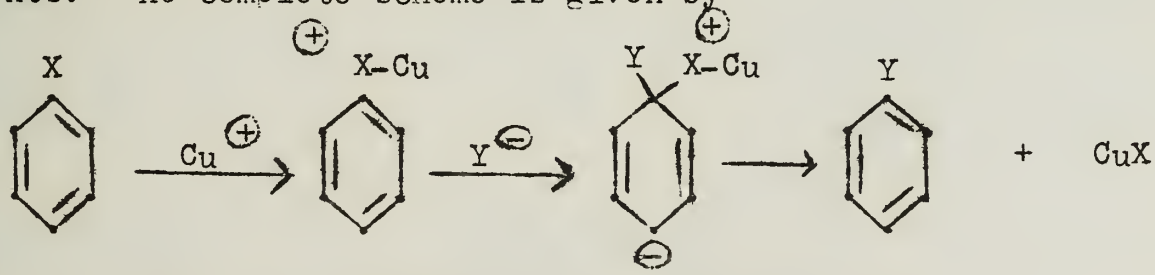
The amount of catalyst required is exceedingly small, 8 X 10^{-} g. of copper in the form of copper sulfate being sufficient to giv a 97% yield of product in the reaction of 1.6 g. of ortho-chlorobenzoic acid with aniline. Careful purification of starting materials, however, showed that this same reaction would not occur without the presence of a metallic catalyst.[8]

IV. MECHANISM

In addition to the need for the presence of a metallic catalyst, other facts which must be considered in proposing a mechanism for this reaction are the stability of the ortho-chlorine substituent in ortho-chlorobenzoic acids in the presence of high hydroxyl concentration,[3] and the fact that the ortho-chlorine substituent in 2,4-dichlorobenzoic acid reacts with nucleophilic reagents to the complete exclusion of the para-chlorine substituent.[3,11,12]. In evaluating the latter information, however, i should be observed that apparently anomalous "ortho effects" also occur in reactions of other negatively substituted aryl halides with nucleophilic reagents, an example being the reaction of 2-aminoethanol with 2,4-dichloro-1-nitrobenzene to give an 88% yield of 2-(5-chloro-2-nitroanilino)-ethanol.[5]

Bunnett and Zahler[1] have proposed an ionic mechanism in which the copper, reacting in the cuprous oxidation state, coordinates with the halogen substituent, converting it to an onium state, It is postulated that this increases the reactivity of the halogen substituent, by analogy with the enhanced reactivity of stable onium compounds, such as ammonium compounds, with nucleophilic reagents. The complete scheme is given by

(2)



where X is halogen and $Y^{\ominus}$ is a nucleophilic reagent.

This representation does not account for any of the previously mentioned peculiarities of the reaction. In view of this, Goldberg has proposed that the reaction proceeds by way of a non-ionized six-membered copper chelate complex (Fig. 1.). It is postulated

that by thereby including participation of the carboxyl group, the greater reactivity of an ortho-halogen substituent over a para-halogen substituent is explained. In this connection it is also of interest to observe that ethyl o-bromobenzoate, p-bromobenzoic acid, and o-bromonitrobenzene will not react with the sodium derivatives of certain active methylene compounds, in the presence of a copper catalyst, under the same conditions that cause o-bromobenzoic acid to react.[4]

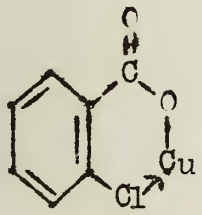
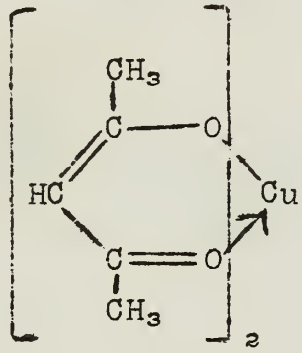


Fig. 1.



IV

An attempt is made to correlate this proposed mechanism with the previously described effect of high hydroxyl concentration, by comparing the yield of 2-carboxy-4-methyldiphenylamine from the copper catalyzed reaction of o-chlorobenzoic acid and p-toluidine in amyl alcohol, with the stability of an amyl alcohol solution of the chelate copper complex of acetylacetone[2] (IV). The effects of adding equivalent amounts of dry K_2CO_3 (insoluble in amyl alcohol), equivalent amounts of dry KOH (soluble in amyl alcohol), and excess aqueous K_2CO_3 were measured. The results observed are summarized in Table 1. The results lend some support to the proposed mechanism, but cannot be accepted as a complete proof of it.

Table 1.[3]

Reagent Added	Yield of Reaction	Effect on Stability of Acetylacetone Complex
Equiv. amt. of dry K_2CO_3	85%	Completely stable, even on prolonged heating.
Large amt. of aqueous K_2CO_3	Yield decreases as amt. of aq. K_2CO_3 is increased	Slow decomposition.
Equiv. amt. of dry KOH	No product obtained; 92% recovery of starting acid.	Immediate, complete decomposition.

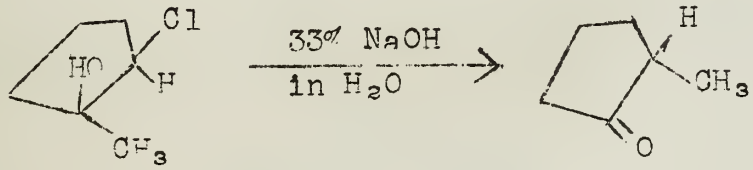
BIBLIOGRAPHY

1. J. F. Bunnett and R. E. Zahler, Chem. Revs. 49, 392 (1951).
2. H. Diehl, Chem. Revs. 21, 63 (1937).
3. A. A. Goldberg, J. Chem. Soc. 1952, 4368.
4. W. R. H. Hurtley, J. Chem. Soc. 1929, 1870.
5. C. B. Kremer and A. Bendich, J. Am. Chem. Soc. 61, 2658 (1939).
6. F. Ullmann, Ber. 36, 2382 (1903).
7. F. Ullmann, Ber. 37, 853 (1904).
8. F. Ullmann, Ann. 355, 312 (1907).
9. F. Ullmann and C. Wagner, Ann. 355, 359 (1907).
10. E. Wenis and T. S. Gardner, J. Am. Pharm. Assoc. 38, 9 (1949).
11. British Patent 353, 537, Apr. 30, 1930, [C.A. 26, 5311 (1932)].
12. German Patent 244,207, Mar. 2, 1910, [C.A. 6, 2293 (1912)].

SOME BASE CATALYZED REARRANGEMENTS

Reported by Y. Gust Hendrickson March 27, 1953

I. Chlorohydrins.--- The treatment of chlorohydrins with base usually gives epoxides. Thus, from trans-2-chlorocyclopentanol, prepared by the addition of hypochlorous acid to 1-methylcyclopentene, 1-methylcyclopentene oxide is obtained. However, the cis isomer, obtained by adding methylmagnesium bromide to 2-chloro cyclopentanone, rearranges to 2-methylcyclopentanone[1].

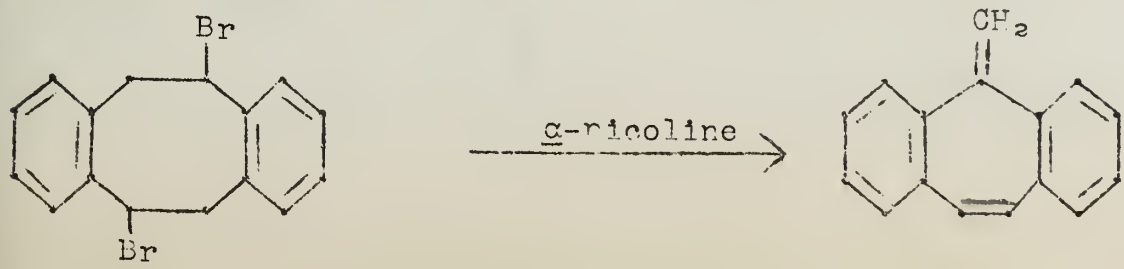


Similar reactions have been observed with the cis isomers of 2-chloro-1-methylcyclohexanol[2], 2-chlorocyclohexanol[3], and 2-chloro-1-indanol[4]; yielding respectively, methyl cyclopentyl ketone, cyclohexanone and 1-indanone. The expected epoxides are obtained with each of the trans isomers. On treatment with sodium methoxide in methanol, the monotosylate of cis-1,2-cyclopentanediol gives cyclopentanone, while the trans isomer gives cyclopentene oxide[5].

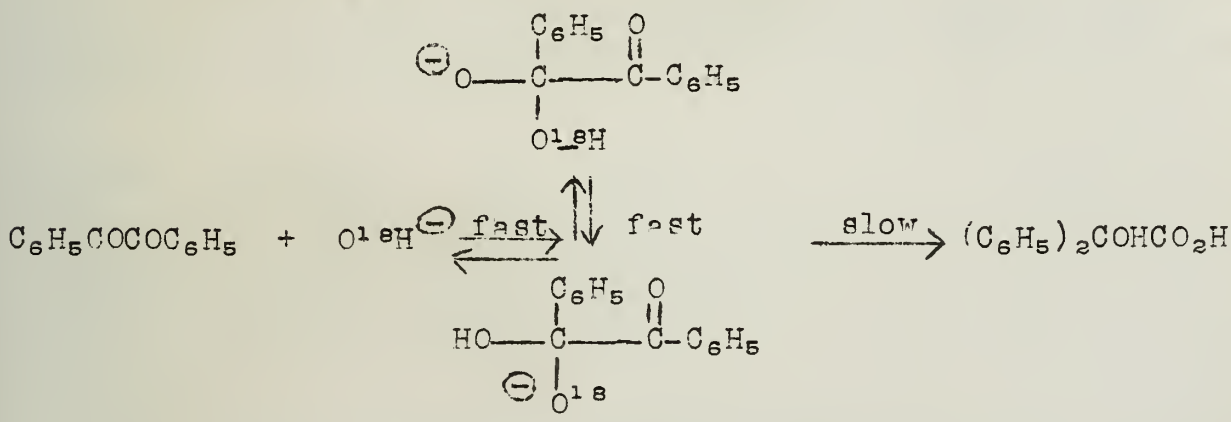
These reactions probably proceed by the abstraction of the hydroxyl proton by the base; followed by the migration of an alkyl group or hydrogen, with its pair of electrons, with subsequent or simultaneous expulsion of chloride or tosylate ion[6,7]. The overall reaction is very similar to the acid catalyzed Wagner-Meerwein rearrangements. The significant difference, however, is that the base catalyzed reaction requires a negatively charged transition state while the acid catalyzed reaction involves a positively charged transition state. The two reactions might, therefore, be expected to show differences in the effects of substituents and in migration aptitudes.

II. Halides.--- Early workers attempting to clarify the isomerism and structures of terpenes came across the rearrangement of bornyl and isobornyl chlorides to camphene, under comparatively mild conditions, with potassium and calcium hydroxides andaniline[8,9,10].

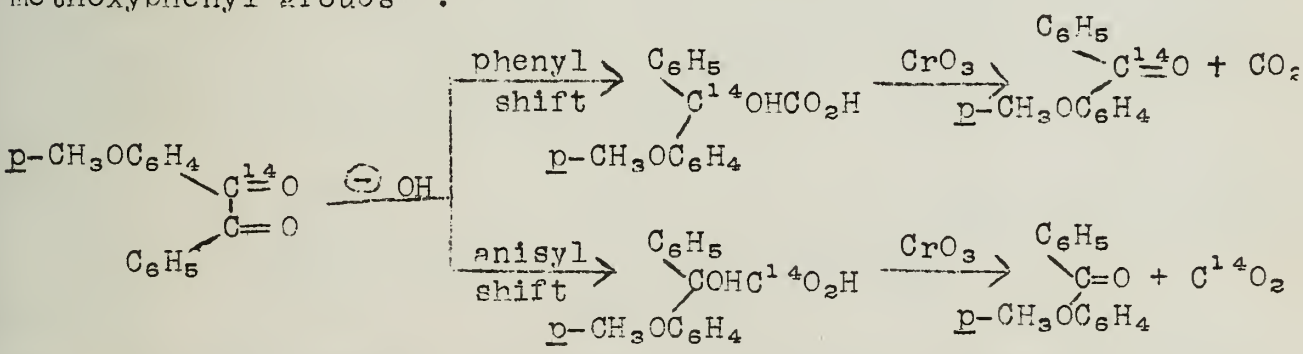
A similar rearrangement was recently observed by Cope and Fenton[11].



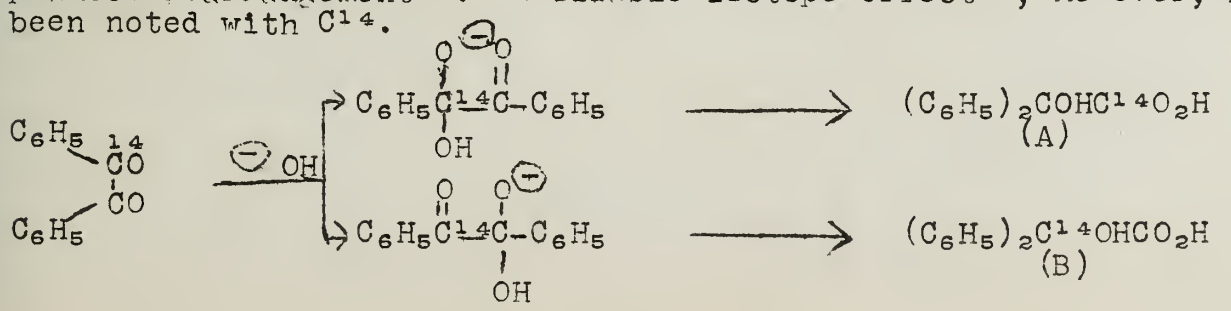
III. Benzilic Acid and Related Rearrangements.--- Benzil yields benzilic acid by a process, the rate of which is first order in both benzil and hydroxide ion[12]. Under conditions which give negligible rearrangement, I. Roberts and H. C. Urey[13] have found that benzil does exchange oxygen with solvent enriched in H_2O^{18} (in neutral aqueous methanol, 43±6% is exchanged in four minutes; 100±6% is exchanged when this solvent is 0.02 N in sodium hydroxide The experiment rules out a mechanism which involves the addition of hydroxide ion to a carbonyl group in the rate determining step. In anhydrous ether, equimolar ratios of benzil and potassium hydroxide yield 81% potassium benzilate[14]. This fact, along with the base catalysis of oxygen exchange noted above, lends support to the mechanism given below.



A recent study of p-methoxybenzil using C^{14} has determined the approximate relative migratory aptitudes of phenyl and p-methoxyphenyl groups[15].



In experiments carried out at 25, 70 and 100°, the ratio of phenyl to p-methoxyphenyl migration was found to be 1.90, 1.72 and 2.17 respectively; as compared with 0.014 found in the acid catalyzed pinacol rearrangement[16]. A sizable isotope effect[17], however, has been noted with C^{14}.

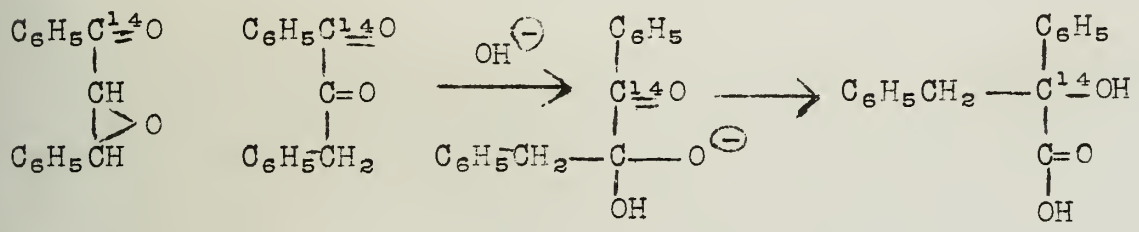


The ratio of A to B obtained was 1.11 ± 0.01.

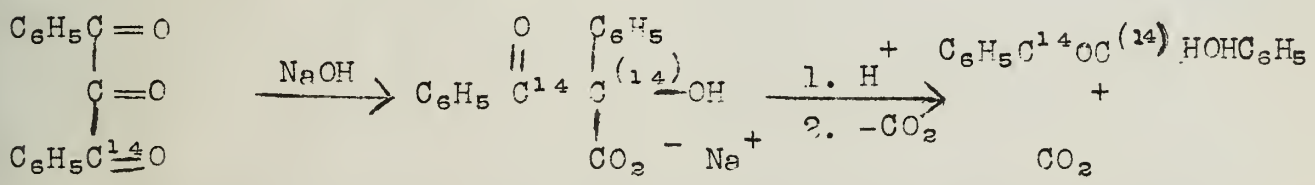
By heating with sodium t-butoxide in benzene solution, some aliphatic diketones (RCOCOR where R is isopropyl, t-butyl and neopentyl) have been rearranged to the corresponding acids[18]. The formation of the acid rather than the ester suggests the operation of a different mechanism.

The rearrangement of phenylglyoxal to mandelic acid, which takes place by an internal hydrogen shift, resembles the rearrangement of benzil[19,20,21].

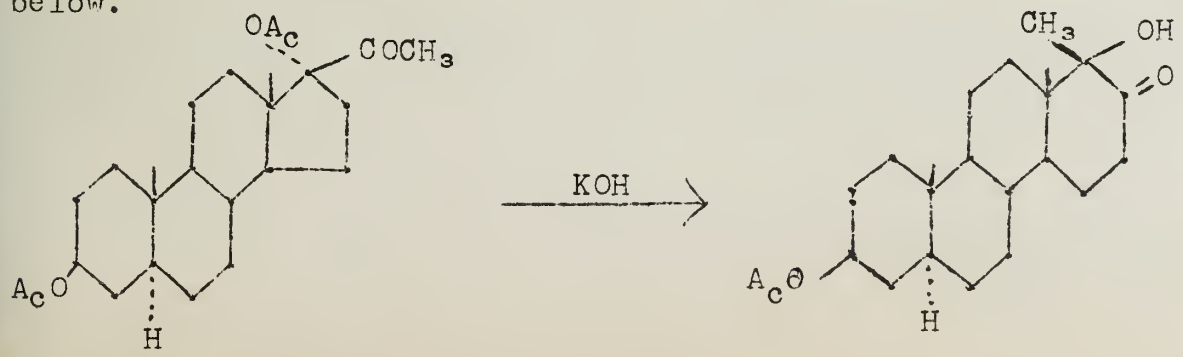
An α-diketone, isolated from the reaction mixture by Baker and Robinson[22], is thought to be an intermediate in the alkaline rearrangement of benzylideneacetophenone oxide. C^{14} has been used to determine benzyl migration[23].



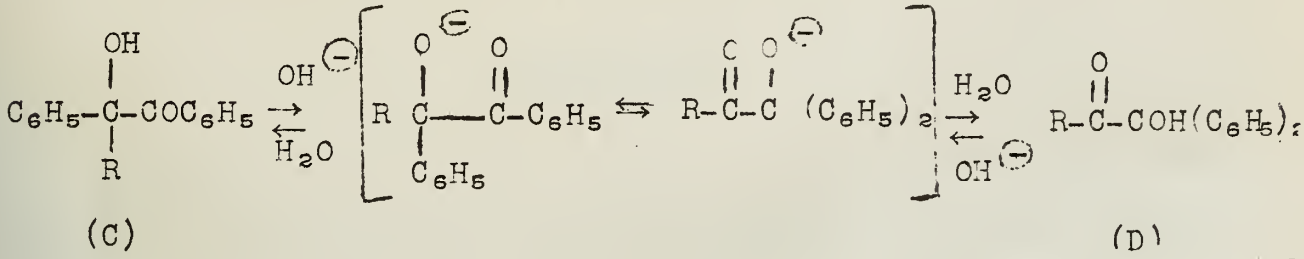
In a dilute solution of sodium hydroxide in aqueous ethanol, diphenyl triketone rearranges, decarbonylates and cleaves to give, on acidification, benzoic acid, mandelic acid (triketone cleavage products), benzoin and carbon dioxide (rearrangement products)[24]. Benzoyl migration and the loss of the center carbonyl have been demonstrated by J. D. Roberts and coworkers[15] with the use of C^{14}. The carbon dioxide obtained was found to be inactive when the triketone was labeled as shown below.



IV. <u>α-Hydroxy Ketones</u>.--- Attempts to saponify 17-acetoxy-20-keto steroids lead to the discovery of a rearrangement which expands the D ring. An example studied by Shoppee and Prins[25] is given below.



Products obtained from the alkaline cleavage of α-substituted benzoins show that a similar rearrangement to isomeric α-hydroxy ketones can take place before splitting occurs. The reaction as pictured by Sharp and Miller[26] follows:

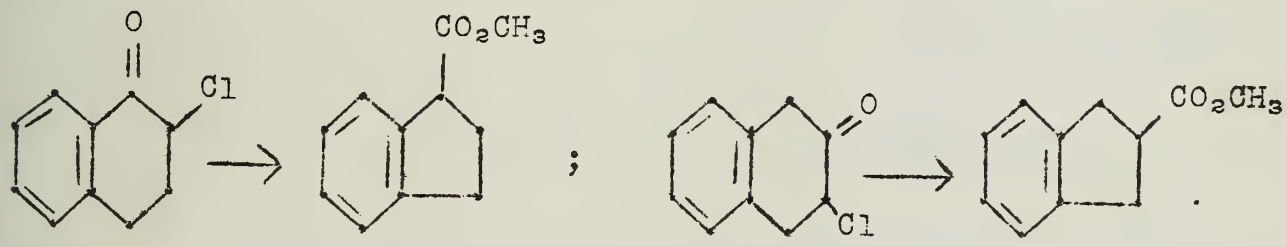


(C) (D)

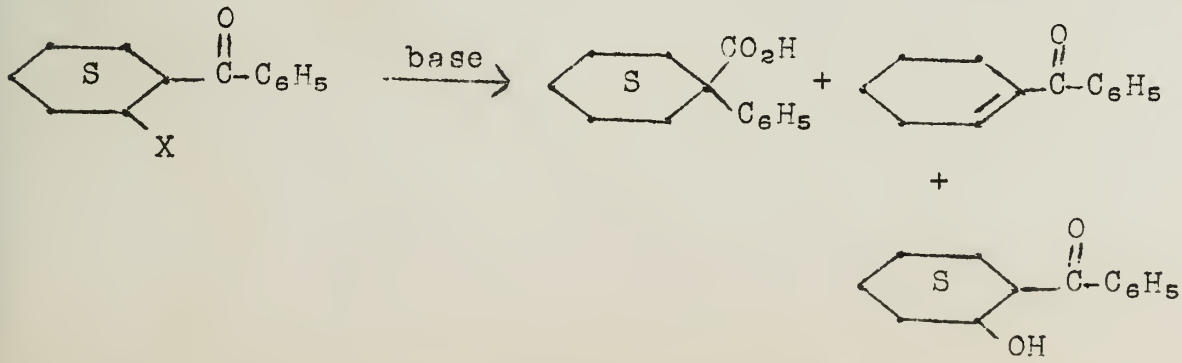
(C) $\xrightarrow{OH^{\ominus}}$ $C_6H_5(R)CHOH$ + $C_6H_5CO_2H$; D $\xrightarrow{OH^{\ominus}}$ $(C_6H_5)_2CHOH$ + RCO_2H

Benzoin gives products that indicate about 27% rearrangement; the methyl and benzyl derivatives show respectively 47 and 40% rearrangement. Although the p-tolyl compound shows only 13% and the m-tolyl, 60-70% rearrangement; only the rearrangement products, in 98% yield, are obtained from α-phenyl and α-o-tolyl benzoins. The aryl compounds were cleaved in refluxing 10% methanolic potassium hydroxide (20% water); methyl and benzyl derivatives required 160°, hence diethylene glycol was used in place of methanol.

V. α-Halo Ketones.--- When α-chlorotetralones are treated with sodium methoxide, a ring contraction occurs[27].



Varying the conditions greatly alters the products formed when α-halocyclohexyl phenyl ketone is treated with base[28].



In refluxing dioxane, with no added based, 8% acid and 60% α,β-unsaturated ketone were isolated. With finely divided sodium

hydroxide vigorously stirred in refluxing xylene as much as 53% rearrangement product and 25% β-hydroxy ketone were obtained. Sodium methoxide in boiling methanol yields the epoxy ether.

BIBLIOGRAPHY

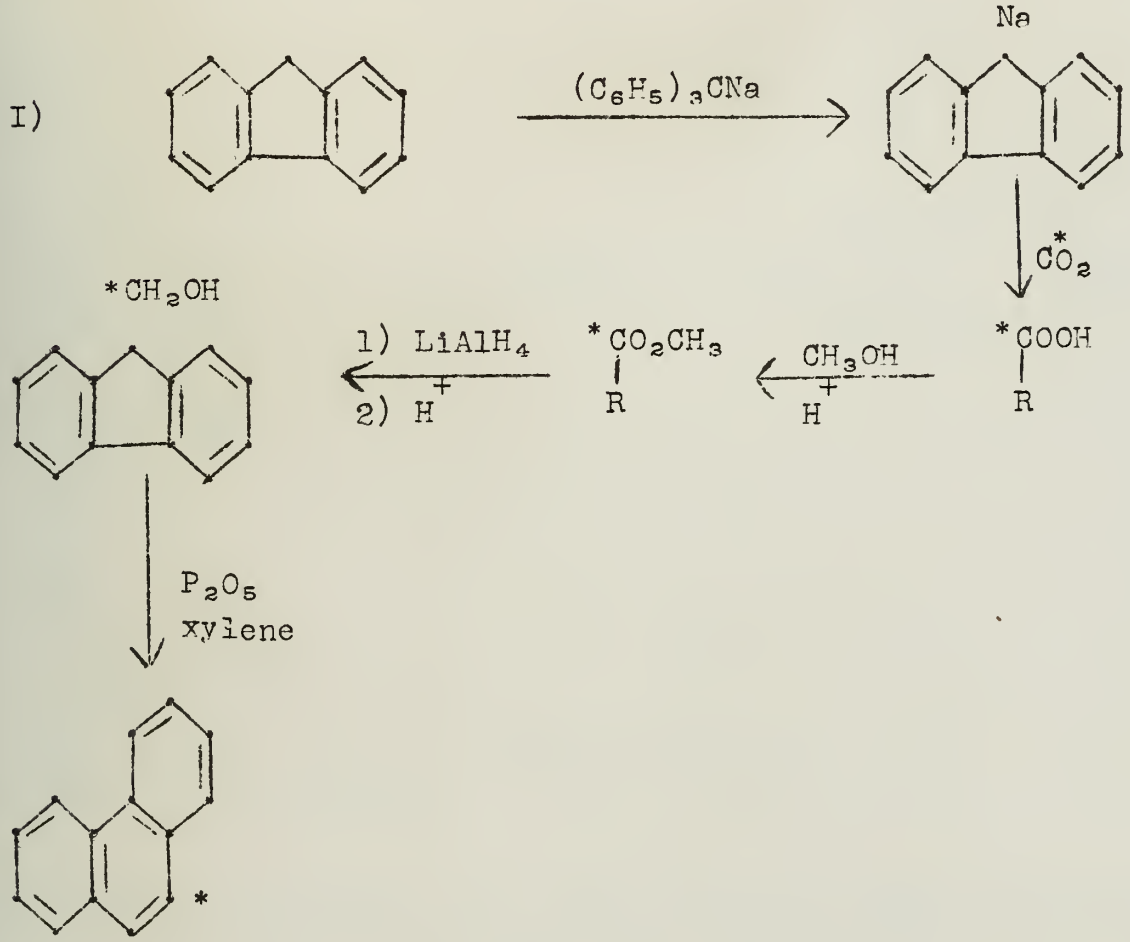
1. P. D. Bartlett and R. V. White, J. Am. Chem. Soc., 56, 2785 (1934).
2. P. D. Bartlett and R. H. Rosenwald, ibid., 56, 1990 (1934).
3. P. D. Bartlett, ibid., 57, 224 (1935).
4. C. M. Suter and G. A. Lutz, ibid., 60, 1361 (1938).
5. L. N. Owen and P. N. Smith, J. Chem. Soc., 1952, 4026.
6. C. K. Ingold, Ann. Repts., 25, 124 (1928).
7. C. R. Hauser, J. Am. Chem. Soc., 62, 933 (1940).
8. O. Wallach, Ann., 230, 233 (1885).
9. O. Aschan, ibid., 410, 222 (1915).
10. A. Reychler, Ber., 29, 696 (1896).
11. A. C. Cope and S. W. Fenton, J. Am. Chem. Soc., 73, 1673 (1951).
12. F. H. Westheimer, ibid., 58, 2209 (1936).
13. I. Roberts and H. C. Urey, ibid., 60, 880 (1938).
14. T. Evans and W. Dehn, ibid., 52, 252 (1930).
15. J. D. Roberts, D. K. Smith and C. C. Lee, ibid., 73, 618 (1951).
16. R. J. Adams, Organic Seminar, Fall Semester 1952, p. 67.
17. W. H. Stevens and R. W. Atree, J. Chem. Phys., 18, 574 (1950).
18. T. S. Oakwood, A. Pohland and J. L. Burhans, Abstracts, 105th Meeting of the American Chemical Society, Detroit, Mich., April 1943, p. 27M.
19. E. R. Alexander, J. Am. Chem. Soc., 69, 289 (1947).
20. W. von E. Doering, T. I. Taylor and E. F. Schoenwalt, ibid., 70, 455 (1948).
21. O. K. Neville, ibid., 70, 3499 (1948).
22. W. Baker and R. Robinson, J. Chem. Soc., 1932, 1798.
23. C. J. Collins and O. K. Neville, J. Am. Chem. Soc., 73, 2471 (1951).
24. R. de Neufville and H. von Pechmann, Ber., 23, 3375 (1890).
25. C. W. Shoppee and D. A. Prins, Helv. Chim. Acta, 26, 185 (1943).
26. D. B. Sharp and E. L. Miller, J. Am. Chem. Soc., 74, 5643 (1952).
27. M. Mousseron and N. Phuoc Du, Compt. rend., 218, 281 (1944).
28. C. L. Stevens and E. Farkas, J. Am. Chem. Soc., 74, 5352 (1952).

MIGRATION IN THE WAGNER REARRANGEMENT

Reported by Thomas R. Moore March 27, 1953

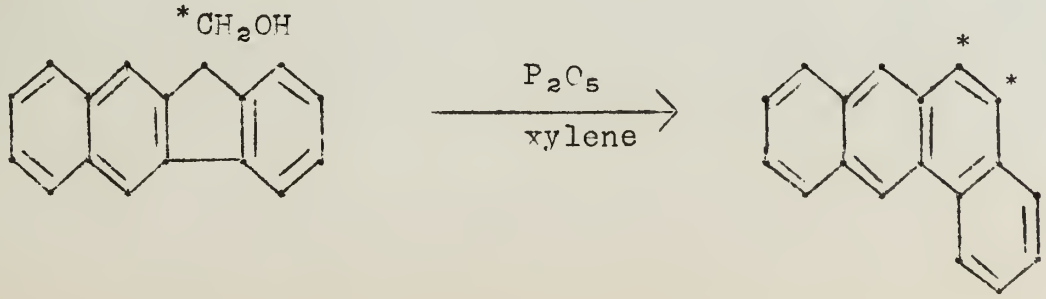
In recent years C. J. Collins and others at the Oak Ridge National Laboratory have been interested in producing C^{14}-labeled polynuclear hydrocarbons. This has been accomplished by means of the Wagner rearrangement. The first synthesis developed was that of phenanthrene-9-C^{14}. The steps in this procedure have been used as models for the syntheses of more complicated molecules and are as follows:[1,2]

I)

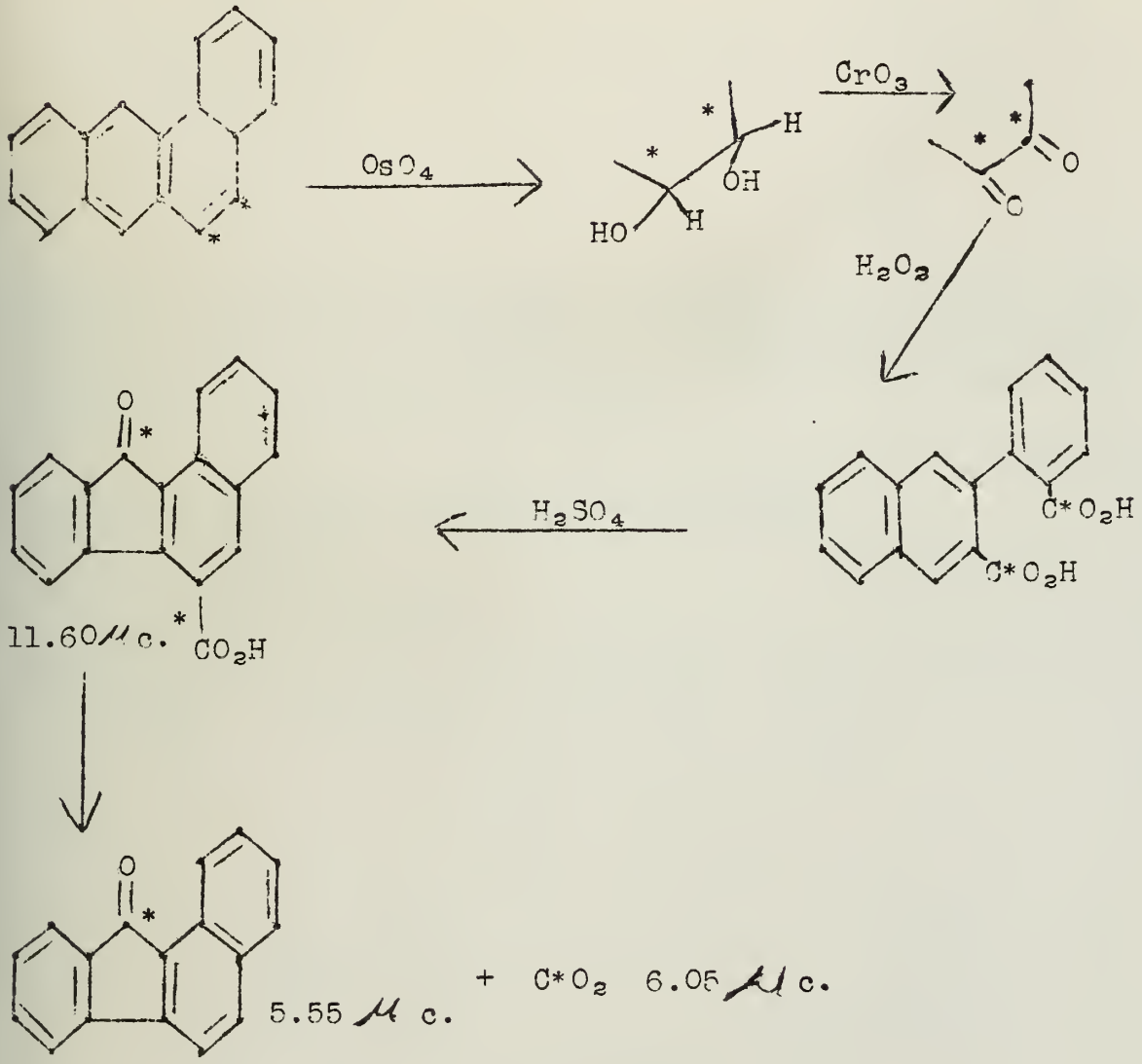


The next compound synthesized in this series was 1,2-benzanthracene,[3] which was made from 2,3-benzofluorene. In this synthesis two different positions could become labeled, depending on the way the Wagner rearrangement proceeded.

II)

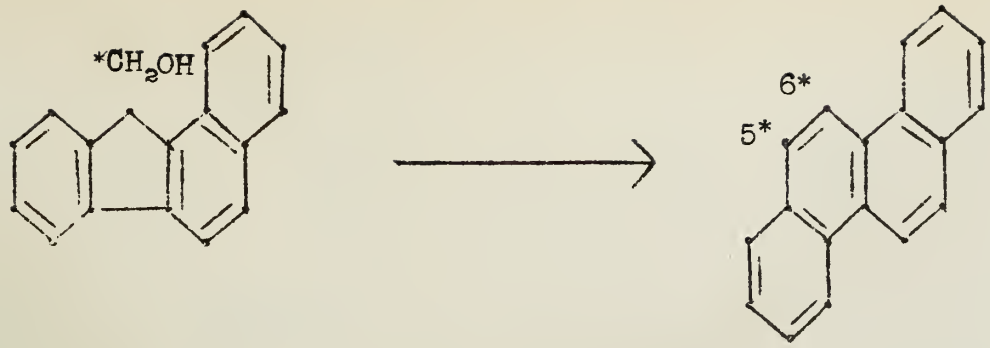


The actual position of the label was determined as follows:



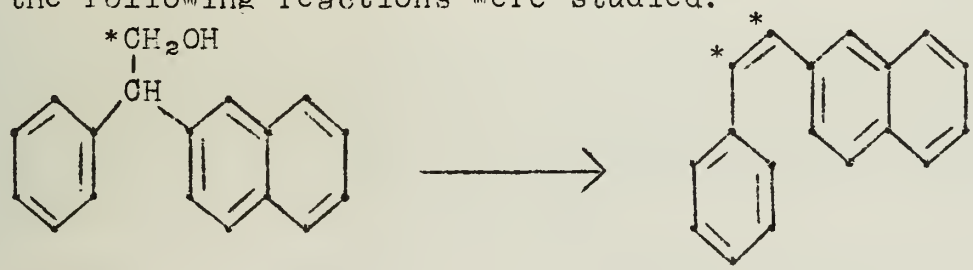
This degradation shows that in the original Wagner rearrangement the ratio of migration of β-naphthyl to migration of phenyl is 52:48. (It is to be noted here that these groups are not really "β-naphthyls" or "phenyls" because of the presence of the biphenyl bond, but such terms can be used to distinguish the groups as well as the more cumbersome correct terms.)

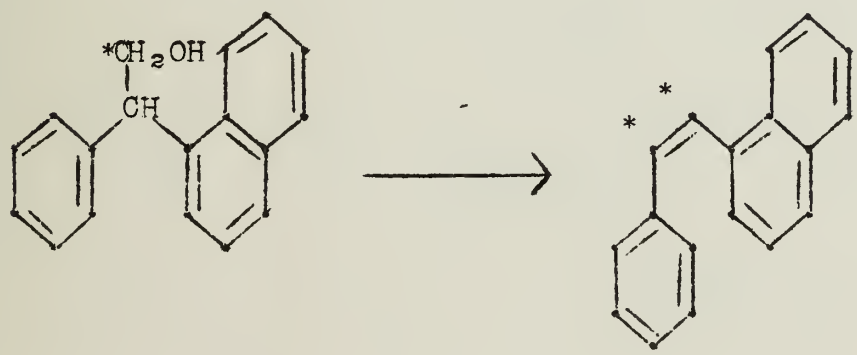
Chrysene-5,6-C_1^{14} was next synthesized[4] from 1,2-benzofluorene by methods similar to those previously described. Here again the label could appear in two places, and the degradations used to determine the actual position of the label showed that the ratio of active carbon in position 5 to that in position 6 is 76:24.

III) 

That the tendency of α-naphthyl to migrate is definitely greater than that of phenyl might have been predicted because of the greater reactivity of the α-position of naphthalene than of the β-position with respect to aromatic substitution, which was theoretically justified by Wheland.[8]

In an attempt to learn more about the nature of these migrations the following reactions were studied:[6]

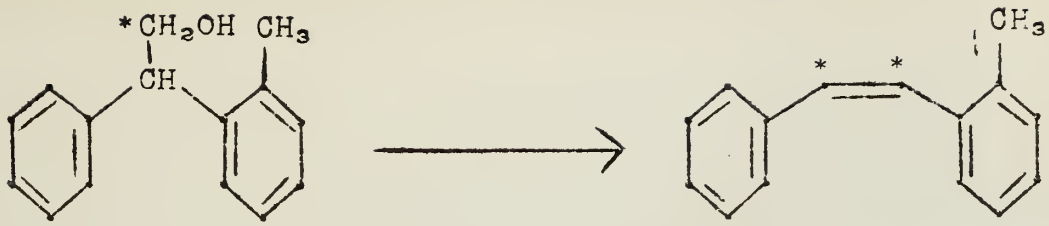
IV) 

V) 

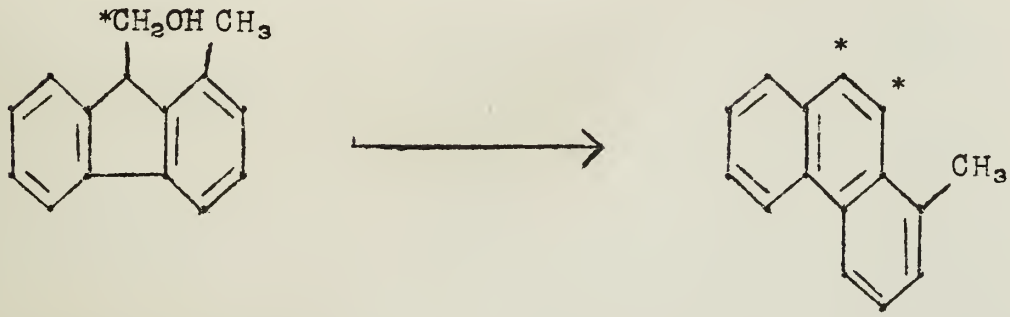
Here it was found that in reaction IV the ratio of β-naphthyl migration to phenyl migration was 56:44. In reaction V the ratio of α-naphthyl migration to phenyl migration was 52:48. Comparison of these results with those of reactions II and III shows that the presence of the biphenyl bond enhances the ability of the α-naphthyl group to migrate in preference to the phenyl group. However, the chance of migration of the β-naphthyl is lessened slightly when the biphenyl bond is present. These results have not yet been satisfactorily explained.

Work was then undertaken which it was hoped would give information on the steric effect of an ortho group.[5] The following reactions were studied:

VI)



VII)



Degradative studies show that the ratio of phenyl migration to that of o-tolyl in reaction VI is 55:45, while in reaction VII it is 50:50. Since this represents a real difference and is not within the range of experimental error, it would seem that the relative migratory aptitudes vary when different systems undergo the same reaction.

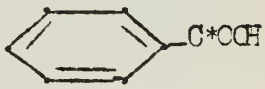
Burr and Ciereszko[9,10] have studied reactions of the type:

VIII) $Ar-CH(*CH_2OH)-C_6H_5 \xrightarrow{H^+} Ar-C^*H{=}C^*H-C_6H_5$

and

IX) $Ar-CH(*CH_2NH_2)-C_6H_5 \xrightarrow{HONO}$ [mixed carbinols] $\xrightarrow{P_2O_5} Ar-C^*H{=}C^*H-C_6H_5$

$Ar-C^*H{=}C^*H-C_6H_5 \xrightarrow[OH^-]{KMnO_4}$

[mixed carbinols] $\xrightarrow[OH^-]{KMnO_4}$ HOOC-  -C*OOH

For these reactions the results are tabulated below.

Ar	PER CENT OF MIGRATION OF Ar	
	Reaction VIII	Reaction IX
p-Diphenylyl	57	50
m-Tolyl	61	48
p-(2-Propyl)-phenyl	65	
3,4-Dimethylphenyl	66	
p-Tolyl	66	47
p-Ethylphenyl	69	
p-(t-Butyl)-phenyl	76	
p-Methoxyphenyl	96	59

This table makes it evident that the relative rates of migration differ in different reactions.

Thus it seems that the relative migratory aptitudes of various groups in carbonium ion reactions are functions of both the type of system used and the reaction involved.

REFERENCES

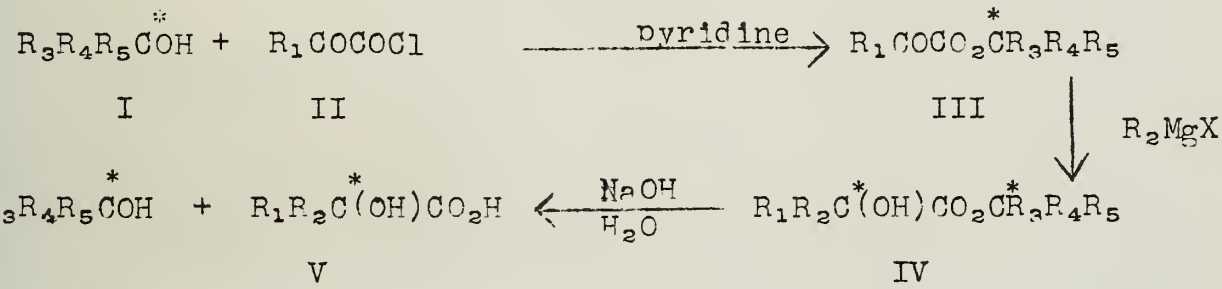
1. C. J. Collins, J. Am. Chem. Soc., 70, 2418 (1948).
2. W. G. Brown and B. Bluestein, ibid., 62, 3256 (1940).
3. C. J. Collins, J. G. Burr, D. N. Hess, ibid., 73, 5176 (1951).
4. C. J. Collins, D. N. Hess, R. H. Mayor, G. M. Toffel, A. R. Jones, ibid., 75, 397 (1953).
5. B. M. Benjamin, C. J. Collins, ibid., 75, 402 (1953).
6. C. J. Collins, L. S. Ciereszko, J. G. Burr, ibid., 75, 405 (1953).
7. E. D. Hughes, C. G. LeFevre, R. J. W. LeFevre, J. Chem. Soc., 202 (1937).
8. G. W. Wheland, J. Am. Chem. Soc., 64, 900 (1942).
9. J. G. Burr and L. S. Ciereszko, ibid., 74, 5426 (1952).
10. L. S. Ciereszko and J. G. Burr, ibid., 74, 5431 (1952).

CONFIGURATION STUDIES BY ASYMMETRIC SYNTHESIS

Reported by Edwin J. Strojny March 27, 1953

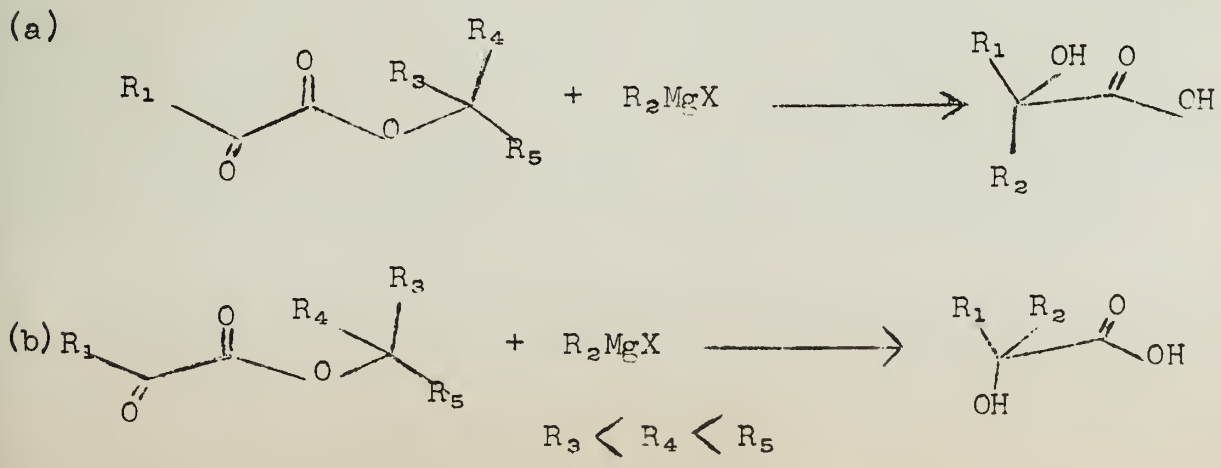
Recently, a method for the determination of the absolute configuration of an asymmetric carbon containing a hydroxyl group has been developed which is based on the asymmetric course of the reaction between a Grignard reagent and an alpha-ketoacid ester.[1,2,3] The rules used in this procedure, propounded by Prelog, were derived from the asymmetric syntheses studies of McKenzie and coworkers[1] and are analogous to those of Curtin and Cram which were discussed in the recent seminar by Passer.[4] The object of this seminar is the presentation of this method as it is applied to the configuration studies of natural products.

The reaction sequence used for the configuration studies is shown here:



By this scheme, an excess of one of the enantiomorphs of the alpha-hydroxyacid is formed. The enantiomorphs are not separated, but rather the direction of the optical rotation of the ethanolic solution of the mixture is noted and the configuration of the alcohol (I) is deduced. The percentage of excess of the alpha-hydroxyacid is readily determined by multiplying the ratio of the specific rotation of the mixture to the specific rotation of the pure enantiomorph by 100. The ketoacid and the Grignard reagent are so chosen that an alpha-hydroxyacid is obtained whose absolute configuration is known. The groups, R_3, R_4, and R_5, of the optically active alcohol are hydrocarbon radicals or hydrogen and must differ appreciably in their spacial requirements in order to alter the steric course of the Grignard reaction sufficiently.

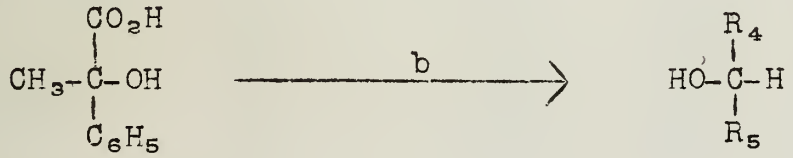
The absolute configuration of the alcohol is derived from the reaction types illustrated below:



The structures of the alpha-hydroxyacid produced in excess are shown. Only the configuration of the asymmetric carbon which contains the hydroxyl group is deduced in this manner.

In his configuration studies by asymmetric synthesis, Prelog used phenylglyoxalic acid and methyl magnesium iodide. These reagents yielded atrolactic acid whose absolute configuration and rotatory power are known. Since his studies involved only secondary alcohols, the reaction types given above can be simplified to the following scheme:

L (+) atrolactic acid in excess $R_4 < R_5$



D (-) atrolactic acid in excess $R_4 < R_5$

Prelog and his co-workers first tested the method by applying it to (-) menthol, (+) neomenthol, (+) borneol and (-) isoborneol. These compounds gave the expected results which are summarized in the table on the next page. The authors then used this procedure for absolute configuration studies on the triterpene alpha-amyrin (VI) and on the steroids dihydrolanosterol (VII) and euphenol (VIII). The phenylglyoxalic acid esters of these three substances induced an asymmetric reaction with the methyl magnesium iodide which yielded, on saponification, a dextrorotatory atrolactic acid in excess. This means that these alcohols belong to the reaction type a and that the asymmetric carbon containing the hydroxyl group would have the configuration corresponding to this type. Such a configuration is in opposition to that arbitrarily assumed for the first two compounds, but is in agreement with the structure assumed for the latter steroid. Other studies with 17 α-androstanol (IX), 7 α- and 7 β-cholestanol (X and XI resp.) showed that the configurations agreed with the previously arbitrarily assumed ones. 3 β-cholestanol (XII) gave only a slight excess of levorotatory atrolactic acid so that no conclusion can be reached with certainty on its configuration by this method.

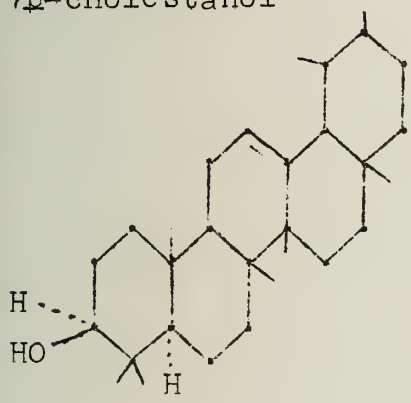
The authors gave certain precautions which should be observed in the application of this procedure. First, complete saponification of the resultant α-hydroxyacid ester must be assured. Prelog has shown that the saponification can proceed asymmetrically so that when only partial hydrolysis is achieved, an excess of the acid opposite in configuration to the ester obtained in excess can

be obtained. Another possible source of error may arise from the fact that the Grignard reagent reacts further with the α-hydroxy-acid ester to produce the glycol. This reaction can also proceed asymmetrically and may impair the results, especially if the yield of the glycol is relatively large. For this reason, little faith is placed on experiments where the optical yield is low. Other phenomena, such as the occurrence of precipitation during the reaction, which may influence the steric course must be avoided.

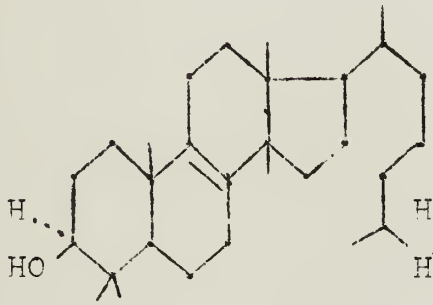
Some Data Obtained by Asymmetric Syntheses

Atrolactic acid $[\alpha]_D = 37.7^\circ$ in alcohol

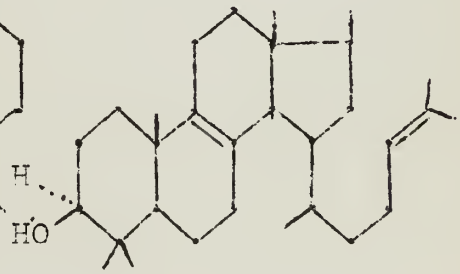
Alcohol	Type	Yield	$[\alpha]_D$	p% (excess)
(-)menthol	b	92%	-9.5	25
(+)neomenthol	a	94	+4.6	12
(+)borneol	a	90	+4.2	11
(-)isoborneol	b	98	-3.1	8.3
α-amyrin	a	71	+3.66	10
dihydrolanosterol	a	58	+13.0	34.5
euphenol	a	82.5	+9.1	24
3β-cholestanol	b?	93	-0.65	1.7
17α-androstanol	a	69.4	+6.2	16.5
7α-cholestanol	b	45.5	-4.8	13
7β-cholestanol	a	86	+26	69



VI



VII



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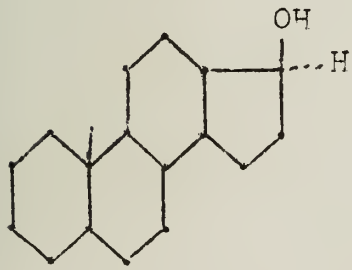
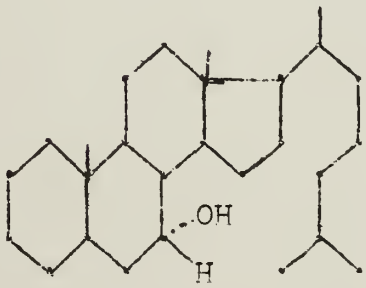
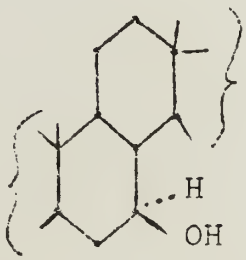


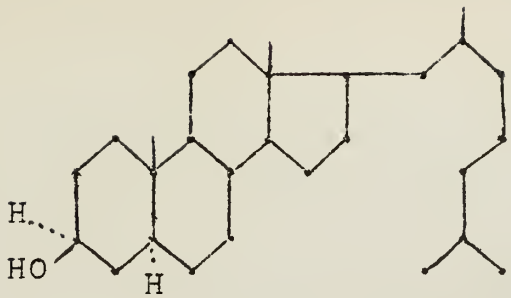
IX



X



XI



XII

BIBLIOGRAPHY

1. Prelog, Helv. Chim. Acta, 36, 308 (1953).
2. Prelog, and Meier, ibid., 320 (1953).
3. Dauben, Dickel, Jeger, and Prelog, ibid., 325 (1953).
4. Seminar Abstracts, University of Illinois, February 20, 1953.

SOME POLYPHENYL DERIVATIVES OF NONMETALLIC ELEMENTS IN THEIR HIGHER VALENCE STATES

Reported by M. J. Fletcher April 10, 1953

Although compounds such as triphenylphosphorus have been known for a long time, it is only in the last few years that polyphenylated compounds of these elements in their higher valence states have been made.

Compounds of the Type $(C_6H_5)_5$ Z (1)(2)(3)

Preparation

$$(C_6H_5)_3\ P = O + C_6H_5\ Li \rightarrow (C_6H_5)_4\ P - OH$$
$$(C_6H_5)_4\ P - OH + H\ I \rightarrow (C_6H_5)_4\ P\ I$$
$$(C_6H_5)_4\ P\ I + C_6H_5\ Li \rightarrow (C_6H_5)_5\ P + Li\ I$$

where Z = P, As, or Sb. The yields from the last step are 60%, 65% and 77% respectively.

$$(C_6H_5)_3\ As\ Cl_2 + 2C_6H_5Li \xrightarrow{Et_2O} (C_6H_5)_5\ As \quad 47\%$$

$$(C_6H_5)_3\ Bi\ Cl_2 + 2C_6H_5Li \xrightarrow{Et_2O} (C_6H_5)_5\ Bi \quad 81\%$$

$$(C_6H_5)_3\ Sb\ Cl_2 + 3C_6H_5Li \xrightarrow{-75^\circ} [(C_6H_5)_6\ Sb]\ Li$$

$$H_2O$$

$$(C_6H_5)_5\ Sb$$

Stability

The stability of these compounds with respect to heat and most acidic reagents increases in the following order:

$$Bi < P < As < Sb$$

The preparation of pentaphenyl bismuth must be carried out at -75°. It precipitates from the ether solution as a yellow solid which changes on warming to a violet powder. The other compounds in this series are colorless. On being heated to 105°, pentaphenylbismuth decomposes vigorously. All the compounds in this series decompose at their melting points.

$$(C_6H_5)_5\ P \xrightarrow{124^\circ} C_6H_5 + \text{Resin}$$

$$(C_6H_5)_5\ As \xrightarrow{150^\circ} C_6H_6 + (C_6H_5)_3\ As\ (81\%) + C_6H_5 - C_6H_5$$

$$(C_6H_5)_5\ Sb \xrightarrow{200^\circ} (C_6H_5)_3\ Sb\ (96\%) + C_6H_5 - C_6H_5\ (98.5\%)$$

$$(C_6H_5)_5\ Bi \xrightarrow{105^\circ} C_6H_6\ (25\%) + C_6H_5 - C_6H_5\ (44\%) + (C_6H_5)_3\ Bi\ (81\%)$$

This decomposition seems to go by a free radical mechanism. Pentaphenyl phosphorus is a good catalyst for the polymerization of styrene.

These compounds are all insoluble in water and easily soluble

in organic solvents, indicating that their bond linkages are covalent.

Reactions:

1) Pentaphenylantimony reacts very readily with one mole of phenyllithium to give a complex salt which is unstable toward water.

$$(C_6H_5)_5\ Sb + C_6H_5\ Li \longrightarrow [(C_6H_5)_6\ Sb]\ Li \xrightarrow{H_2O} (C_6H_5)_5Sb + C_6H_6 + LiOH$$

2) These compounds react with halogens to yield, in most cases, tetraphenyl metal perhalides.

$$(C_6H_5)_5\ P + Br_2 \longrightarrow (C_6H_5)_4\ P\ Br_3 + C_6H_5Br$$

$$(C_6H_5)_5\ As + I_2 \longrightarrow (C_6H_5)_4\ As\ I_3 + C_6H_5I$$

$$(C_6H_5)_5\ Bi + 2Br_2 \xrightarrow{-70^\circ} (C_6H_5)_4\ Bi\ Br_3 + C_6H_5\ Br$$

$$\downarrow \text{warming to } -30^\circ$$

$$(C_6H_5)_3\ Bi\ Br_2 + C_6H_5\ Br$$

$$(C_6H_5)_5\ Sb + Br_2 \rightarrow \underset{\text{isolable}}{(C_6H_5)_4\ Sb\ Br} \xrightarrow{Br_2} (C_6H_5)_4\ Sb\ Br_3$$

$$\downarrow 130^\circ$$

$$(C_6H_5)_3\ Sb\ Br_2 + C_6H_5\ Br$$

However: $(C_6H_5)_5\ Sb + Cl_2 \longrightarrow (C_6H_5)_4\ Sb\ Cl$

$$\downarrow \underset{C_6H_6}{\text{boiling}}\ Cl_2$$

$$(C_6H_5)_3\ Sb\ Cl_2 + C_6H_5Cl$$

$(C_6H_5)_4\ Sb\ Cl_3$ has not yet been prepared.

3) Reactions with halogen acids

$$(C_6H_5)_5\ Z + HX \rightarrow (C_6H_5)_4\ Z\ X + C_6H_6$$

where Z is P or as

$$(C_6H_5)_5\ Sb + HBr \rightarrow \underset{\text{isolable}}{(C_6H_5)_4\ Sb\ Br} \xrightarrow{HBr} (C_6H_5)_3\ Sb\ Br_2 + C_6H_5Br$$

$$(C_6H_5)_5\,Bi + HCl \xrightarrow[-70^\circ]{\text{dry ether}} (C_6H_5)_4\,Bi + C_6H_6$$

$$\downarrow \text{warming to } -20^\circ$$

$$(C_6H_5)_3\,Bi + C_6H_5\,Cl$$

These reactions appear to be ionic.

These compounds also react with Lewis acids such as triphenyl boron

$$(C_6H_5)_5\,Z + (C_6H_5)_3\,B \xrightarrow[\text{ether}]{} [(C_6H_5)_4\,Z]^{\oplus}\,[(C_6H_5)_4B]^{\ominus}$$

$$\downarrow$$

Tetraphenyltellurium (4)

The only tetraphenyl derivative of an element in the fourth group which has yet been prepared is tetraphenyltellurium

$$(C_6H_5)_2\,Te\,Cl_2 + C_6H_5\,Li \rightarrow [(C_6H_5)_3\,Te\,Cl]$$

$$\downarrow C_6H_5\,Li$$

$$(C_6H_5)_4\,Te + Li\,Cl$$

Tetraphenyl tellurium is less stable than pentaphenylphosphorus. It is also decomposed by water

$$(C_6H_5)_4Te \longrightarrow (C_6H_5)_2\,Te + C_6H_5\text{-}C_6H_5 + C_6H_6$$

$$(C_6H_5)_4\,Te + H_2O \longrightarrow (C_6H_5)_3\,Te\,OH + C_6H_6$$

It forms a stable complex with triphenyl boron.

$$(C_6H_5)_4\,Te + (C_6H_5)_3\,B \longrightarrow [(C_6H_5)_3\,Te]\,[(C_6H_5)_4\,B]$$

In its reactions it behaves very much like the Grignard reagent.

$$(C_6H_5)_4\,Te + CH_2Cl_2 \rightarrow (C_6H_5)_3\,Te\,Cl + C_6H_5CH_2Cl$$

$$(C_6H_5)_4\,Te + CHCl_3 \longrightarrow (C_6H_5)_3\,Te\,Cl + C_6H_5CHCl_2$$

$$(C_6H_5)_4\,Te + C_6H_5CHO \rightarrow \text{(after hydrolysis)}\,(C_6H_5)_3TeCl + (C_6H_5)_2CHOH$$

Triphenyliodine (1), (4)

Triphenyliodine is the only polyphenyl derivative of an element in the seventh group which has been found isolable.

$$[(C_6H_5)_2I]\ I + C_6H_5Li \xrightarrow[-80^\circ]{} (C_6H_5)_3\ I + Li\ I$$

$$\text{or } C_6H_5I\ Cl_2 + 2C_6H_5\ Li \xrightarrow[-80^\circ]{} (C_6H_5)_3\ I + 2\ Li\ Cl$$

This compound is very unstable at temperatures as low as -10°. After drying in a vacuum, however, it can be kept awhile at 2°. It explodes on being brought to room temperature.

It forms the expected complex with triphenyl boron, which is stable at room temperature.

$$(C_6H_5)_3\ I + (C_6H_5)_3\ B \rightarrow [(C_6H_5)_2\ I\ ]\ [(C_6H_5)_4\ B\ ]\downarrow$$

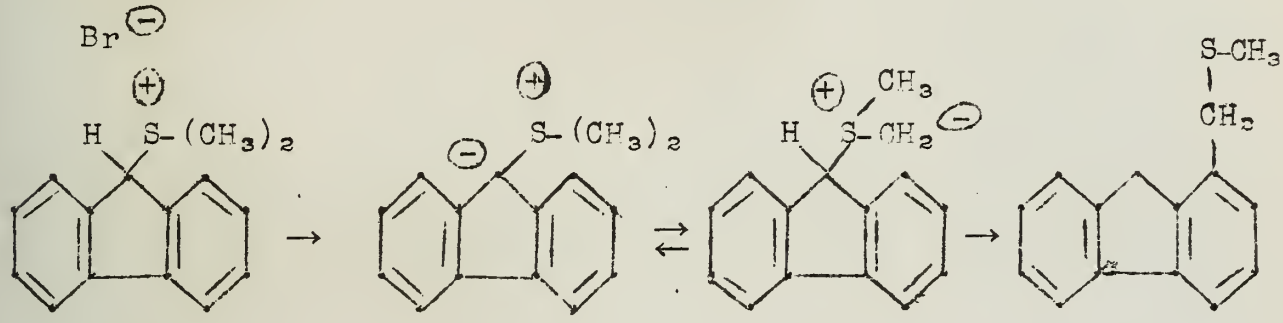
BIBLIOGRAPHY

1. G. Wittig and M. Rieber, Ann., 562, 187 (1949).
2. G. Wittig and K. Clauss, Ann., 577, 26 (1952).
3. G. Wittig and K. Clauss, Ann., 578, 136 (1952).
4. G. Wittig and H. Fritz, Ann., 577, 39 (1952).

REARRANGEMENTS OF 9-SUBSTITUTED FLUORENES

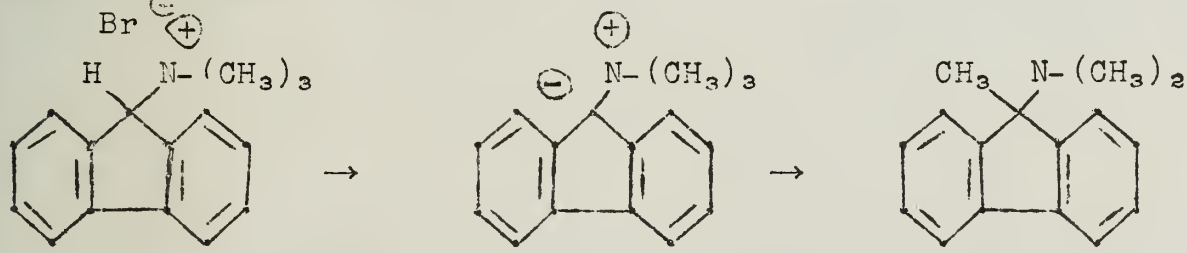
Reported by Richard L. Johnson April 10, 1953

The first report of a rearrangement of a 9-substituted fluorene compound was by Hilbert and Pinck[1] in 1938. They reports that dimethyl-9-fluorenyl sulfonium bromide (I) was transformed in the presence of alkali to an equilibrium mixture of ylid-like compounds[2]. One of these (II) was stable, while the other (III) rearranged to form methyl-(1-fluorenylmethyl)-sulfide (IV). This reaction differs from all subsequent rearrangements of this type in that the alkyl group migrates to the 1- rather than to the 9-fluorenyl position. This difference is explained by the assumption that compound II is stable, and that compound III is the reactive species.



I II III IV

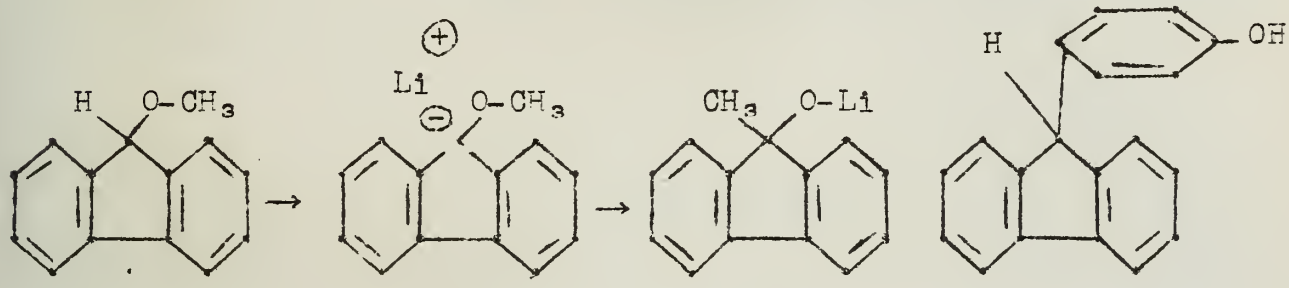
Wittig and Felletschin[3] found that 9-fluorenyl trimethylammonium bromide (V) when treated with phenyllithium produced a stable fluorenylid (VI). When this ylid was heated it rearranged to form 9-methyl-9-dimethylaminofluorene (VII). The reaction of 9-fluorenylbenzyldimethylammoniumbromide was also carried out in the same manner. The product, formed in nearly quantitative yields, was 9-benzyl-9-dimethylaminofluorene. This fact demonstrates that the benzyl group migrates in preference to the methyl group in this reaction.



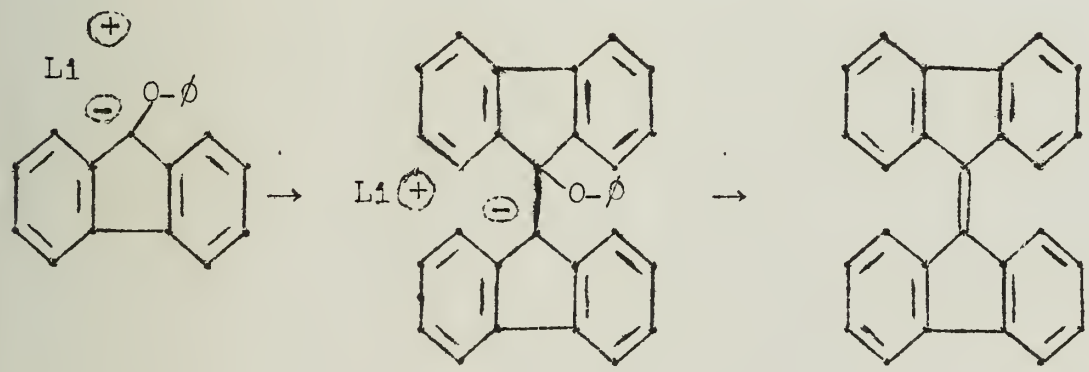
V VI VII

Wittig and Felletschin also studied the rearrangement of 9-fluorenyl methyl ether. This reaction had been suggested by similar reactions of benzyl ethers which had been studied earlier[4]. When the ether (VIII) was treated with phenyllithium, intermediate IX formed and rearranged to X which could be hydrolyzed to 9-methyl-9-fluorenol. Rearrangement of other 9-fluorenyl ethers was also studied[5]. Phenyllithium was found to be the most effective catalyst in these rearrangements, and tetrahydrofuran was found to be a suitable solvent[6]. The ethyl and allyl ethers were made by the same method as the methyl ether: fluorene was brominated by

N-bromosuccinimide, and the product was treated with silver nitrate and the appropriate alcohol. The benzyl ether was prepared from 9-bromofluorene and benzyl alcohol with no catalyst. The phenyl ether could not be prepared from 9-bromofluorene and either phenol or potassium phenoxide. These reagents produced 9-(p-hydroxyphenyl)-fluorene (XI) and bidiphenyleneethylene (XIV) respectively. When 9-bromofluorene, phenol, and potassium phenoxide were refluxed in tetrahydrofuran the desired ether was obtained. In like fashion the p-methylphenyl-, p-chlorophenyl-, p-iodophenyl-, p-nitrophenyl-, and p-trimethylammoniumphenyl-ethers were prepared



VIII IX X XI

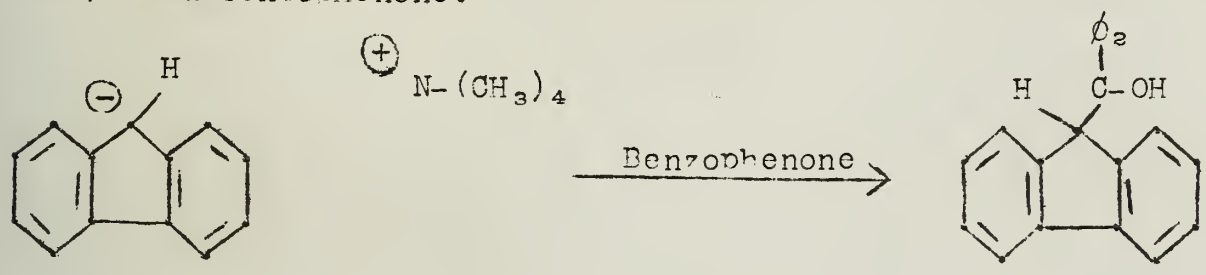


XII XIII XIV

The rearrangement of these ethers was carried out under a nitrogen atmosphere. The lithium derivatives of the ethers were prepared by the addition of phenyllithium. The ethyl and methyl ethers produced lithium derivatives stable at room temperature. When these derivatives were heated at 100°C. for four hours, they rearranged to the corresponding 9-alkyl-9-fluorenols. The allyl and benzyl ethers produced lithium derivatives which rearranged at once to the expected fluorenols. The lithium derivative of di-9-fluorenyl ether rearranged at once, forming 9-fluorenyl-9-fluorenol. When phenyl fluorenyl ether was treated with phenyl lithium, a lithium derivative formed which was stable at room temperature but which rearranged at 100°C. to form bidiphenyleneethylene (XIV) and potassium phenoxide. This reaction occurs through intermediates XII and XIII, which have been isolated.

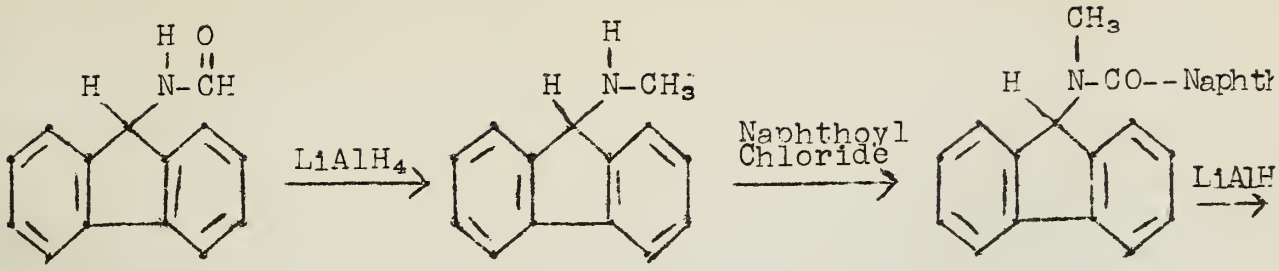
The para-substituted phenyl ethers, with the exception of the p-nitro compound, also formed bidiphenyleneethylene. The p-nitrophenyl fluorenyl ether, bearing an electron-withdrawing substituent, rearranges, as the alkyl ethers do, when it is treated with lithium methoxide at 100°C.. Lithium methoxide was used instead of phenyllithium to prevent reduction of the nitro group.

In another series of experiments Wittig, Heintzler, and Wetterling[7] produced "organometallic tetramethylammonium compounds" from organometallic compounds and tetramethylammonium halides. Among the carbanions so formed was that from 9-bromofluorene (XV). These compounds were ionic salts. The 9-fluorenyl compound rearranged when heated, forming 9-methylfluorene. The salt reacted as an organometallic compound, forming 9-fluorenyldiphenyl carbinol (XVI) from benzophenone.



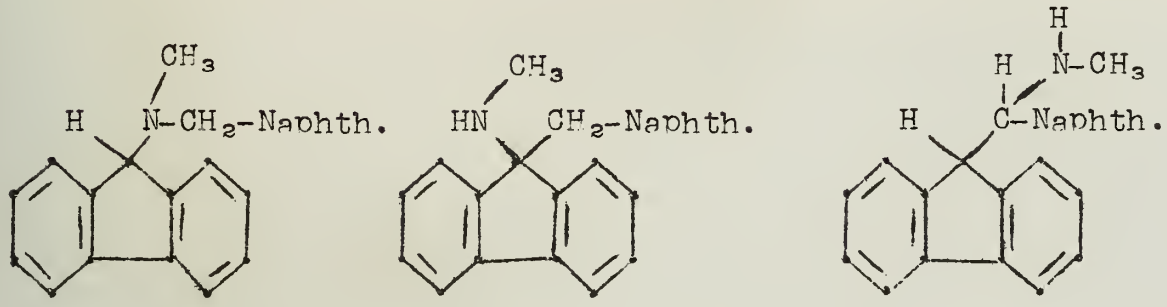
XV XVI

Dahn and Solms[8] have reported the rearrangement of tertiary amines. They were attempting to synthesize 9-fluorenylnaphthoylmethylmethyl amines (XX α. and β.). The route of synthesis is shown (XVII through XX). The reactions proceeded as shown when diethyl ether was used as solvent, but when tetrahydrofuran was used as solvent for the last reaction, an isomeric secondary amine (XXI) was formed in 56% yield. Hydrogenolysis of the secondary amines produced the corresponding 9-fluorenylnaphthylmethanes which were also prepared by independent synthesis. It was found that lithium aluminum hydride in tetrahydrofuran isomerized XX to XXI by acting as a strong base. That the secondary amines were not XXII was not proved, but these structures are unlikely in view of the higher acidity of the 9-fluorenyl hydrogen as compared to the napthoylmethyl hydrogens. This rearrangement could not occur through an ylid intermediate since the amine was secondary. Thus, it more nearly approximates the rearrangements of the ethers.



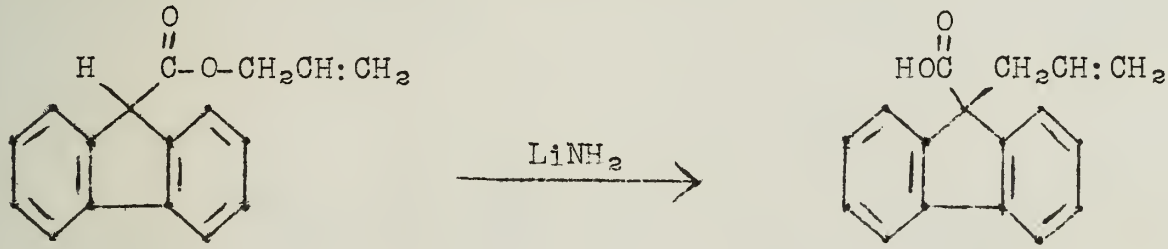
XVII XVIII XIX

α.:Naphth. = α Naphthyl
β.:Naphth. = β Naphthyl



XX (α. and β.) XXI (α. and β.) XXII (α. and β.)

Still another rearrangement of a fluorene derivative has been reported by Arnold, Parham, and Dodson[9]. The allyl ether of 9-fluorenecarboxylic acid (XXIII) was isomerized to 9-allylfluorene-9-carboxylic acid (XXIV) by lithium amide. This type of reaction had been found to occur with diphenylacetic acid esters[10], with a resulting allylic shift. Further publication was promised concerning the rearrangements of benzyl esters, which seemed to give mixtures of products, but none has yet appeared.



XXIII XXIV

BIBLIOGRAPHY

1. Hilbert and Pinck, J. Am. Chem. Soc., 60, 494 (1938).
2. Lovejoy, Organic Seminars, U. of I., I Semester 1951.
3. Wittig and Felletschin, Ann., 555, 133 (1944).
4. Wittig and Lohmann, Ann., 550, 260 (1942).
5. Wittig, Döser and Lorenz, Ann., 562, 192 (1949).
6. Wittig and Happe, Ann., 557, 205 (1947).
7. Wittig, Heintzler and Wetterling, Ann., 557, 201 (1947).
8. Dahn and Solms, Helv., 34, 908 (1951).
9. Arnold, Parham, and Dodson, J. Am. Chem. Soc., 71, 2439 (1949).
10. Arnold et. al., ibid., 71, 1150 (1949).

A NEW SYNTHETIC APPROACH TO o - HYDROXY PHENOL DERIVATIVES

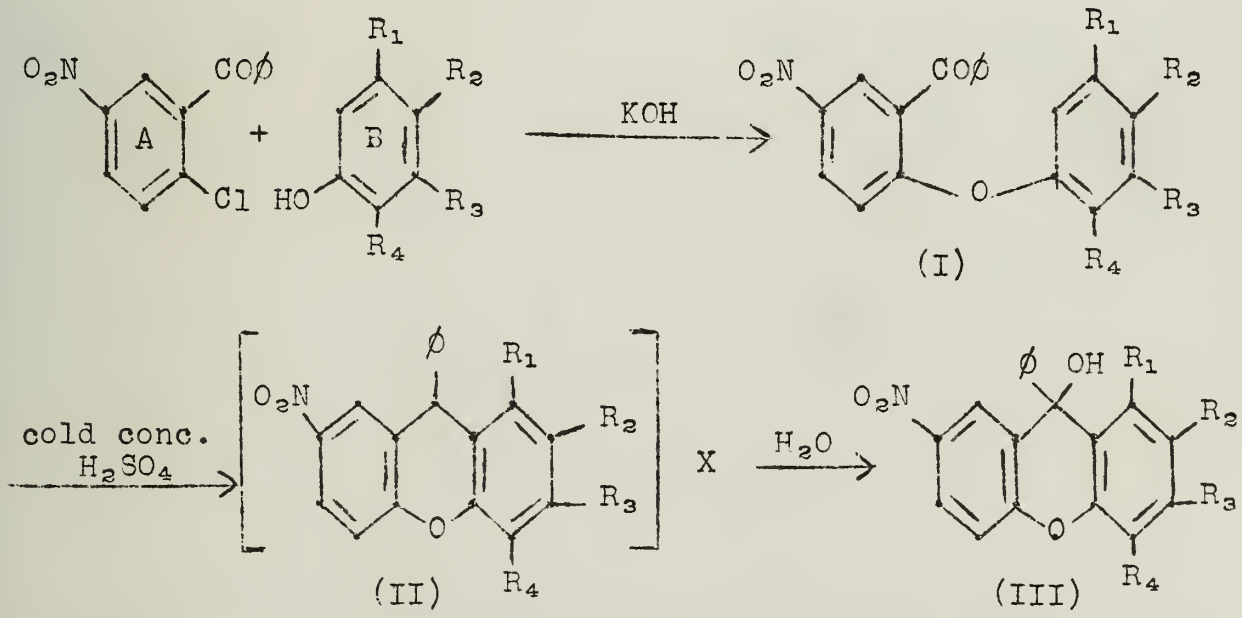
Reported by William H. Lowden April 10, 1953

INTRODUCTION

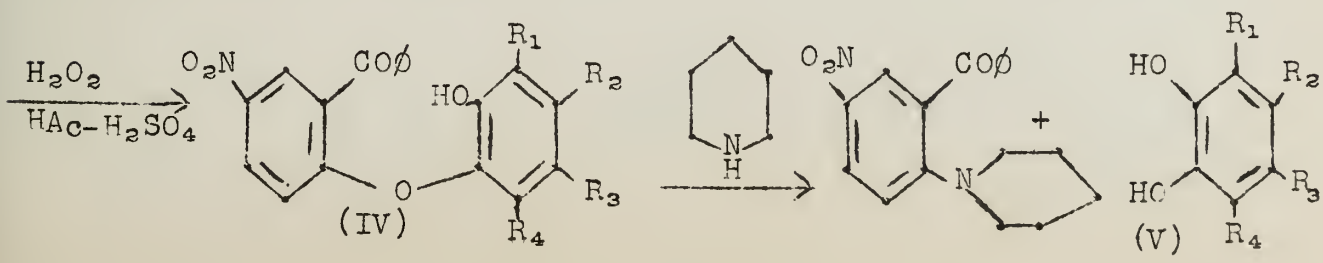
A recently developed method for the synthesis of catechol and pyrogallol derivatives has opened an attractive new route to compounds which were previously obtained with great difficulty. The reaction, in addition to its synthetic value, can also be used advantageously in structure proofs.

SYNTHESIS

2-Chloro-5-nitrobenzophenone and a phenol react in the presence of a base to form a 5-nitro-2-aryloxybenzophenone as would be predicted on the basis of the Williamson ether synthesis. Cyclization to the corresponding xanthylium salt is conducted in the presence of sulfuric acid. Analogous cyclizations have been reported of substituted diaryl ethers and corresponding thio compounds.[1,2] Upon extreme dilution, the xanthhydrol is formed. This material is dissolved in acetic and sulfuric acids with slow addition of hydrogen peroxide. The resulting 5-nitro-2-(2'-hydroxy)-aryloxybenzophenone is then cleaved by piperidine. Similar cleavages have been known since 1927.[3,4] The products isolated are the 2-piperidino-5-nitrobenzophenone and an o-hydroxy phenol corresponding to the original phenol.



9-phenyl xanthylium sulfate

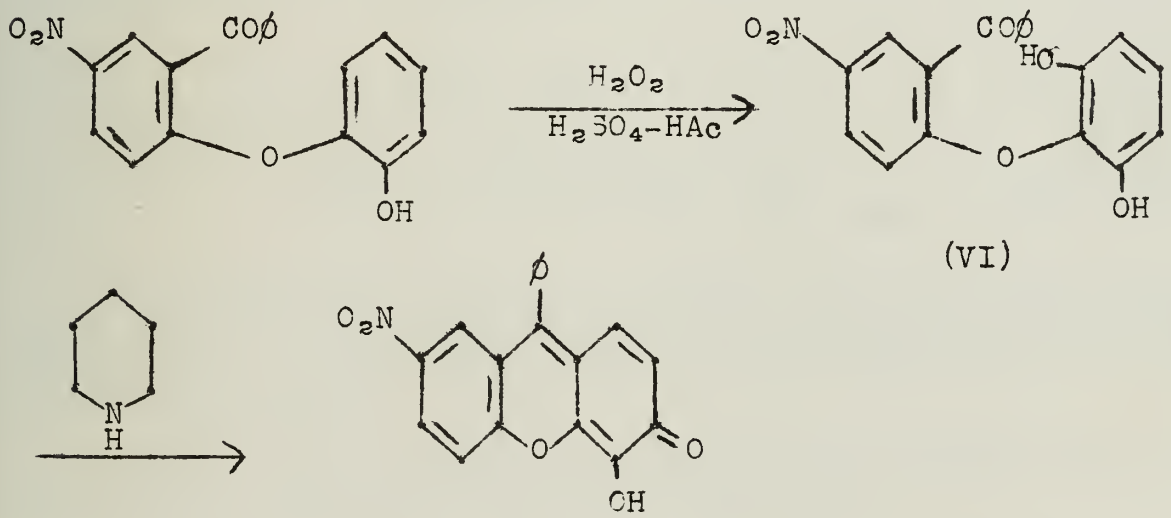


DISCUSSION AND LIMITATIONS

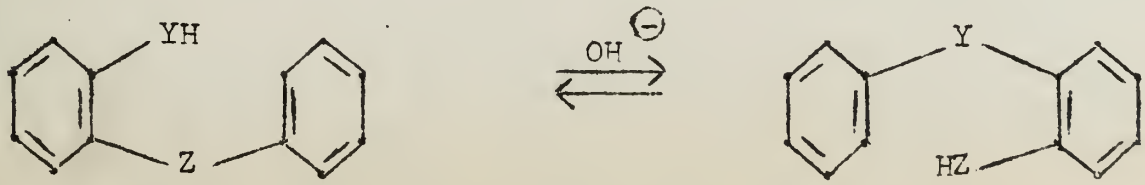
The activity of the chlorine atom in an ortho position to a strong electron acceptor is enhanced by the presence of electron withdrawing substituents on the nucleus.[5] Hence, the aromatic chlorine is sufficiently active to give good yields of the ether in the reaction with a phenol.

The final concentration of sulfuric acid in the cyclization step has proved to be the crucial factor in the synthesis. Similar work on thioxanthene and derivatives has shown that this cyclization is dependent upon the nucleophilic reactivity of ring B.[6]

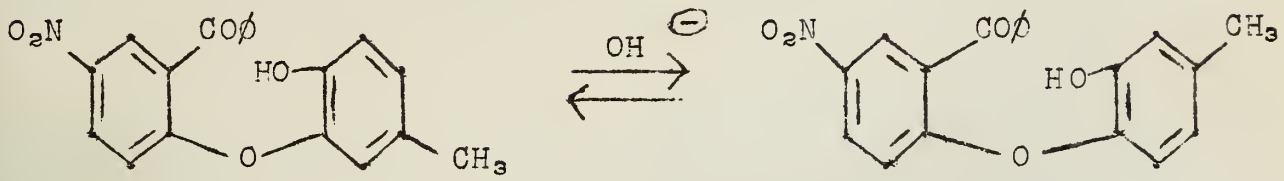
The essential contribution in this series of papers is the choice of the oxidizing medium. Hydrogen peroxide, in a sulfuric and acetic acid mixture, has the ability to introduce a free hydroxyl group in the 2' position under these conditions. The resulting compound, (IV), is cleaved with piperidine yielding the desired phenol. However, in many instances, a rearrangement or a dehydration to a fluorone occurs. Apparently, the dehydration mainly occurs during the removal of the piperidine by acid. Methyl, methoxy or p-toluenesulfonic acid groups (located at R_1 and R_3) prevented the dehydration whereas the bromo derivatives cyclized readily. An example of this cyclization follows:



The rearrangement which takes place in an alkaline solution is similar to the type first observed by Smiles. He has shown that an important factor in the rearrangement is the different electron donor abilities of the atoms Y and Z.

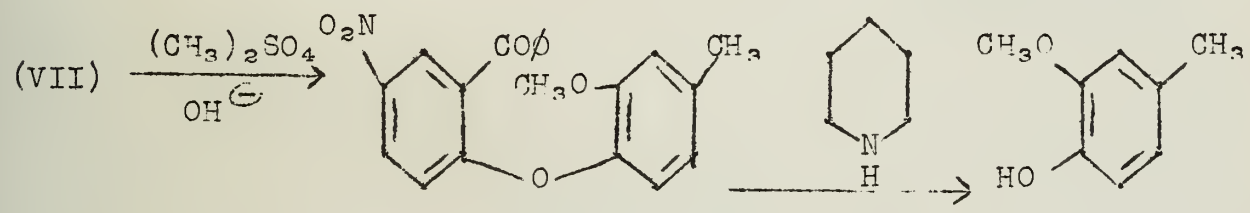


This rearrangement occurs in this series of compounds in the following manner:

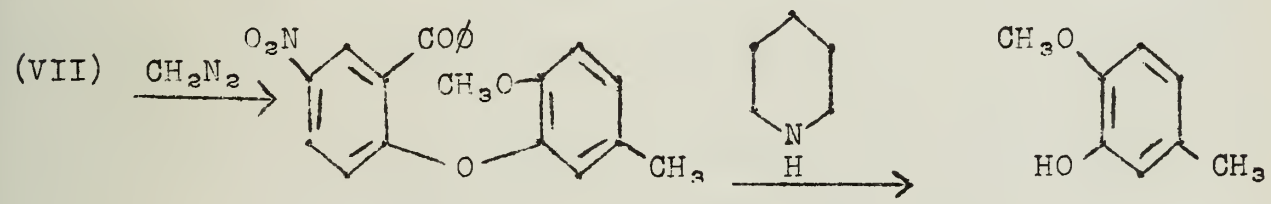


(VII) (VIII)

Conclusive evidence for the rearrangement is obtained upon treatment of (VII) with alkaline methyl sulfate. Rearrangement must, therefore, occur before methylation. Cleavage with piperidine gives rise to the corresponding phenol.

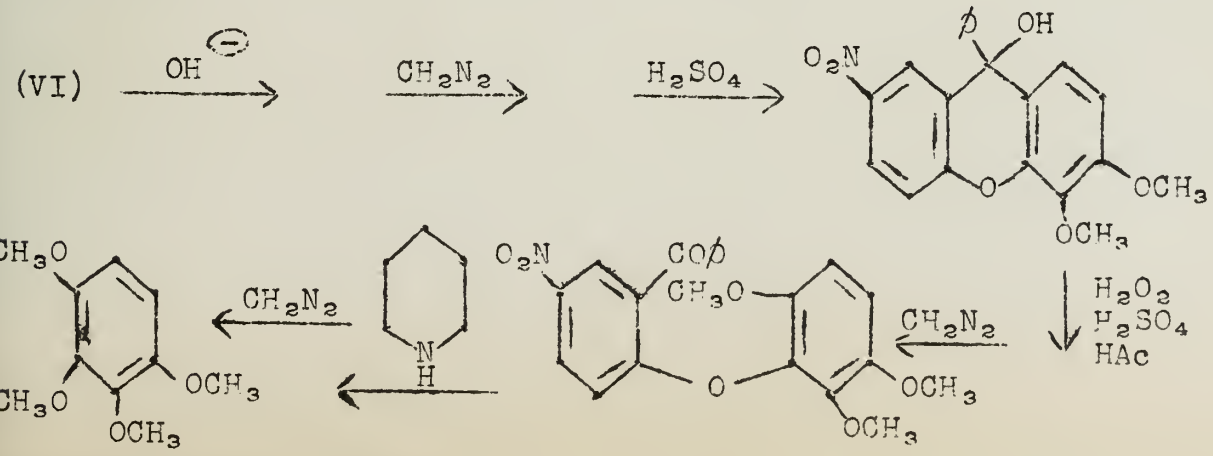


Diazomethane, unlike methyl sulfate and alkali, methylates the compound without rearrangement.



The condensation product of guaiacol and 2-chloro-5-nitrobenzophenone was identical with the methylation product of (IV) (R_1, R_2, R_3, R_4 = H). Hence, there is no doubt as to the nature of the ring opening.

Repeated hydroxylation of a phenol can be accomplished as is shown by the synthesis of tetramethoxybenzene.



Other than the aforementioned limitations, the reaction appears to be quite general, as is exemplified by the following list of compounds prepared in this manner.

catechol
pyrogallol
3,5-dimethylcatechol
3,6- "
4,5- "

3-phenylcatechol

4- "

2-methoxy-3,5-dimethylphenol

2- " 3,6- "
2- " 4,6- "
2- " 5-phenylphenol

3,4-dihydroxytoluene
2-hydroxy-3-methoxytoluene
3- " 2- "
4,6-dimethylpyrogallol
4,6-dibromopyrogallol-1,3-dimethy ether

4,6-dibromo-5-methylpyrogallol-1 3-dimethyl ether

4-hydroxy-7-nitro-9-phenyl-fluorone

3-bromo-4-hydroxy-7-nitro-9-phenylfluorone

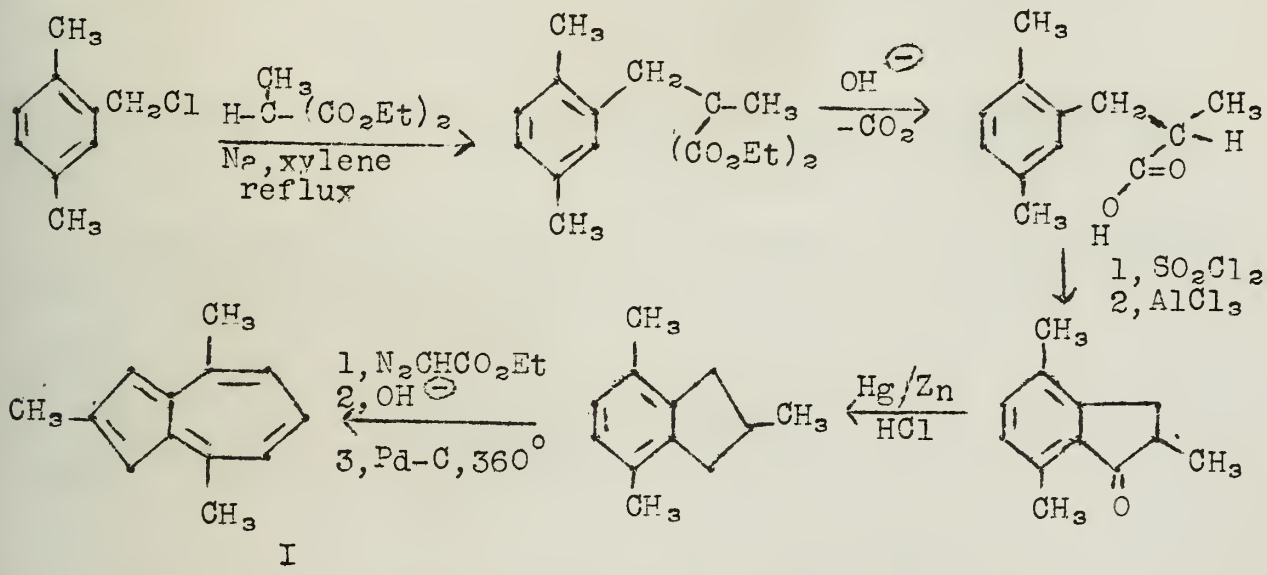
BIBLIOGRAPHY

1. Decker, et.al., Annalen 348, 231, 238 (1906).
2. Reilly, J. and Drumm, P. J., J. Chem. Soc., 1930, 455.
3. Le Fevre, J. W., Saunders, L. M. and Turner, E. E., J. Chem. Soc., 1927, 1168.
4. Groves, L. G., Turner, E. E. and Sharp, G. I., J. Chem. Soc., 1929, 512.
5. Holmes, C. W. N. and Loudon, J. D., J. Chem. Soc., 1940, 1521.
6. Campbell, C. V. T., Dick, A., Ferguson, J., and Loudon, J. D., J. Chem. Soc., 1941, 747.
7. Quint, F. and Dilthey, W., Ber. 64, 2082 (1931).
8. Loudon, J. D., Robertson, J. R., Watson, J. N. and Aiton, S. D., J. Chem. Soc., 1950, 55.
9. Loudon, J. D. and Scott, J. A., J. Chem. Soc., 1953, 265.
10. Loudon, J. D. and Scott, J. A., J. Chem. Soc., 1953, 269.

Reported by Aldo J. Crovetti April 17, 1953

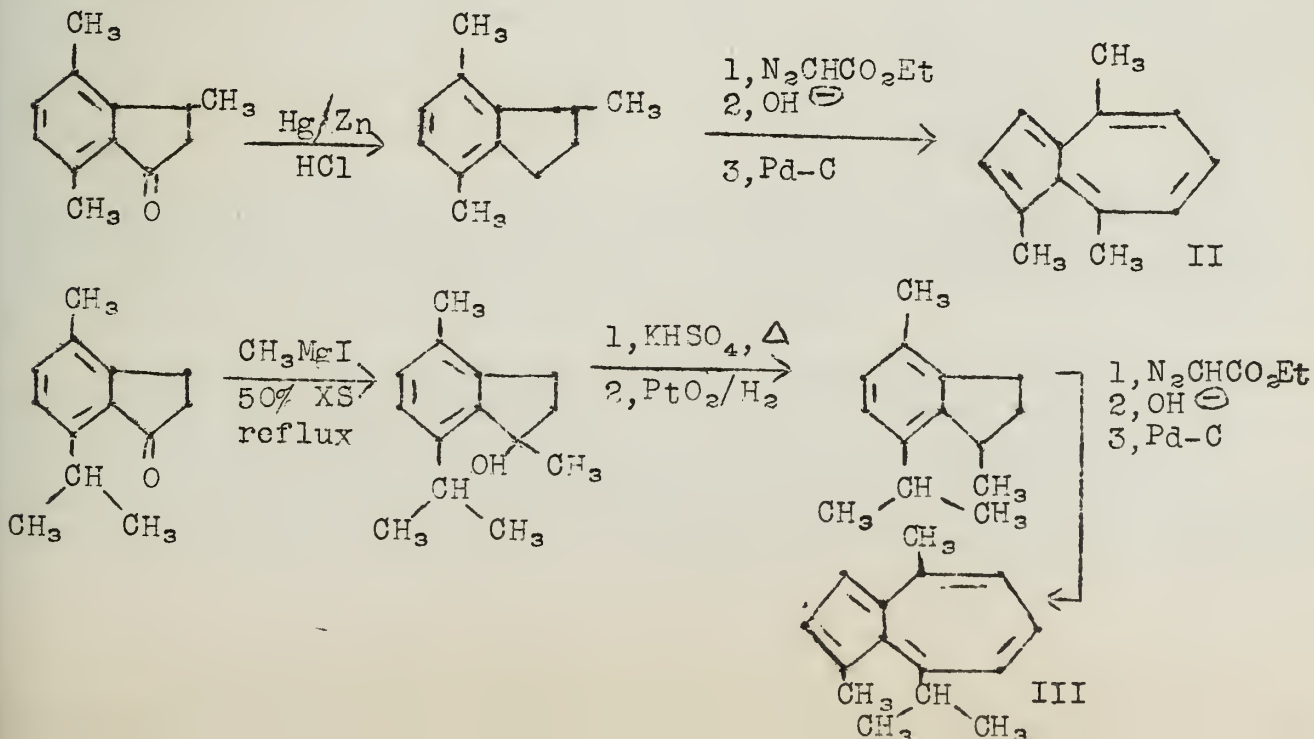
Azulene chemistry has been the subject of many reviews. Most recently it has been extensively reviewed through January 1951 by M. Gordon.[1] Also a recent seminar deals with recent work through 1949.[2] This seminar will deal mainly with work since 1951.

The classical method for azulene synthesis employing ring expansion with diazoacetic ester has recently been exploited by Herz[3,4,5], who has used this method for the preparation of trialkylated azulenes. The synthesis of 2,4,8-trimethylazulene (I) is outlined below.

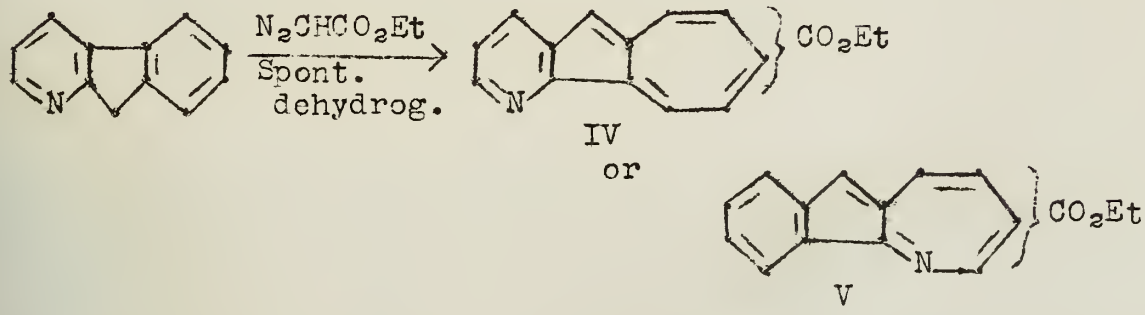


The product did not appear to be indentical with pyrethazulene whose structure was suggested as (I) by Schechter in 1941.

In a similar manner Herz[4] has synthesized 1,4,8-trimethylazulene (II) and 1,4-dimethyl-8-isopropylazulene (III), previously not described.

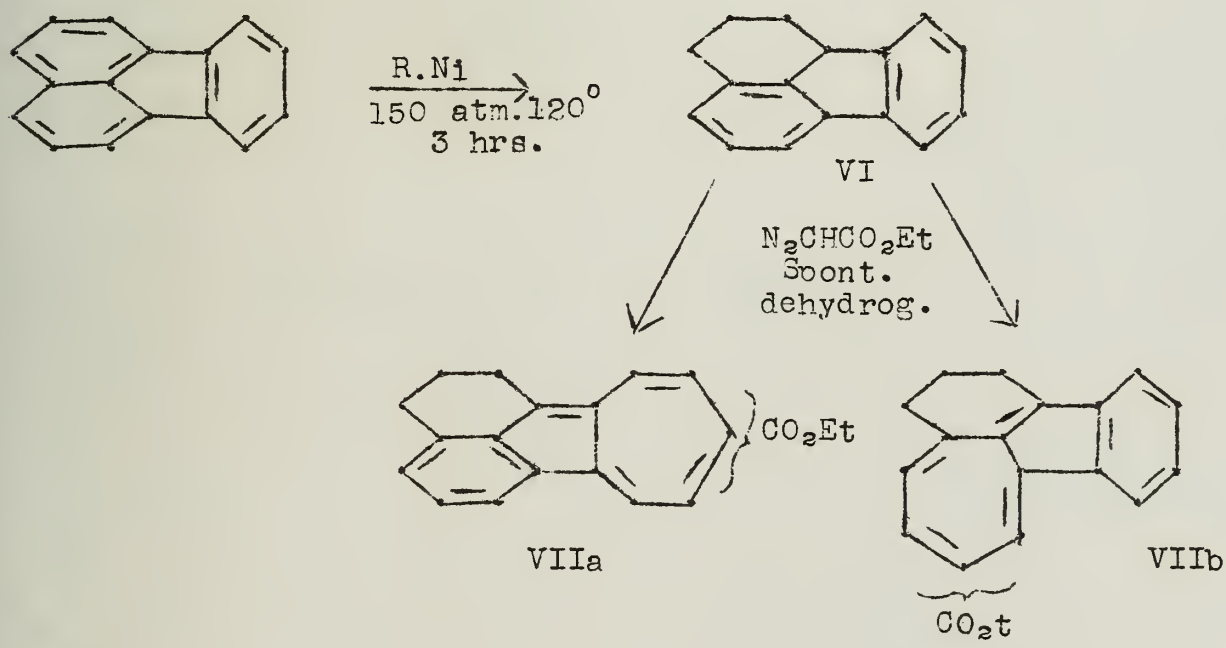


W. Treibs[6] has employed this procedure using 4-azafluorene and obtained an azaazulene (IV) or (V).



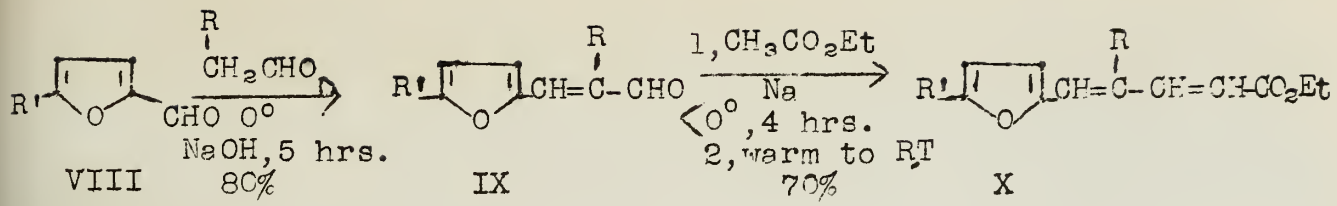
The free acids obtained by saponification at room temperature undergo facile decarboxylation to give products which are less stable to light and air than the carbethoxy derivatives.

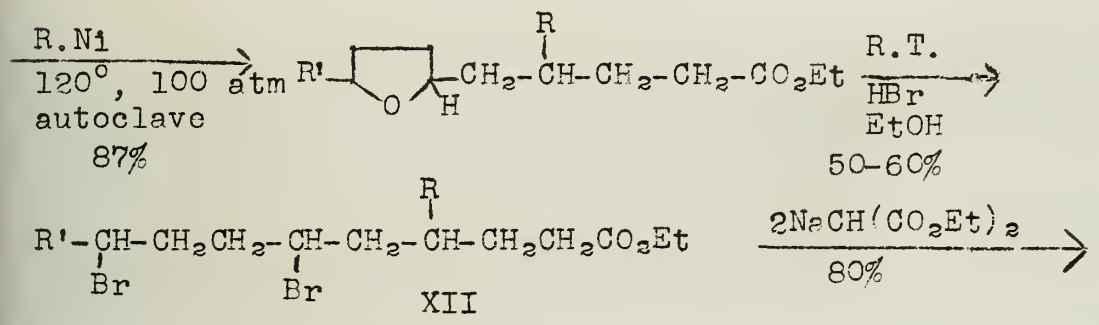
Treibs[7] has also applied this procedure to the synthesis of azulene esters (VIIa) or VIIb) of tetrahydrofluoranthene (VI).

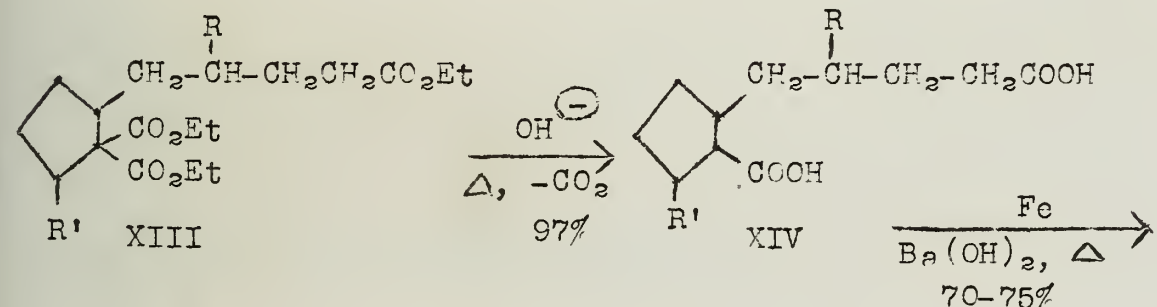


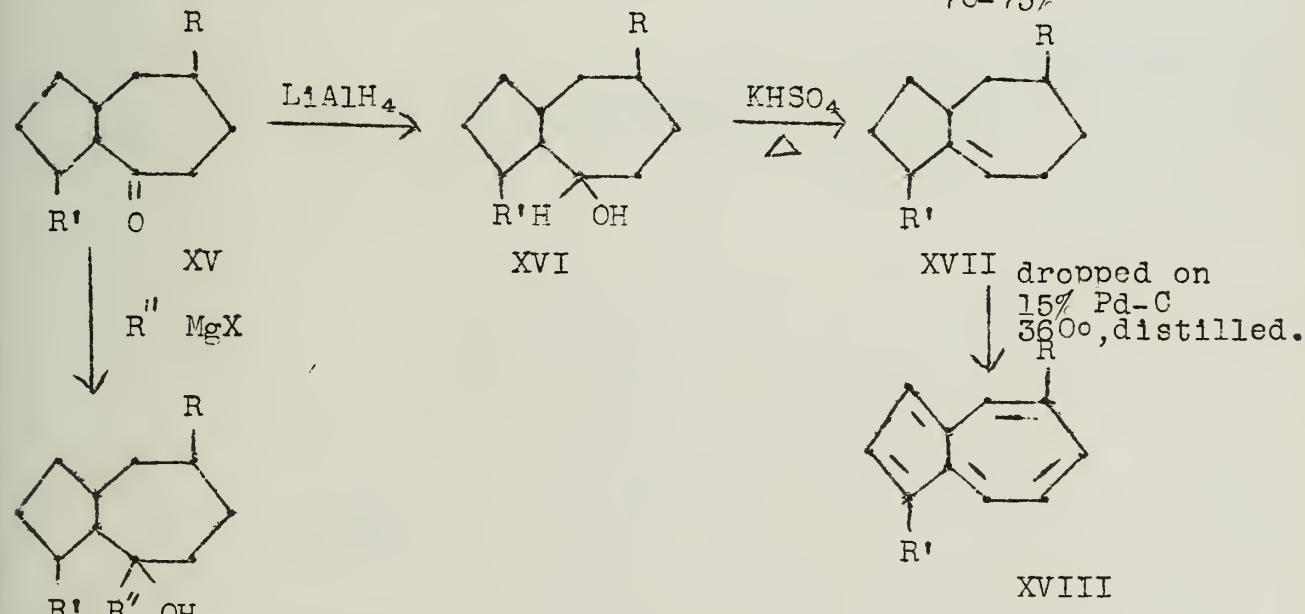
Regarding the position of the ester group it is interesting to note that Plattner[8], using indane and 2-methylindane, was able to separate from the reaction mixture the 5- and 6-carboxylic acid esters, but found no trace of the 4-isomer.

Recently several azulene syntheses have been announced which do not involve ring expansion. H. Pommer[9,10] has developed a promising method for the synthesis of 1,5,8-,1,4,7-,1,7,8-, and 1,4,5-trisubstituted azulenes which heretofore have not been prepared in pure form (if reported at all) due to the complications of ring expansion procedures. The procedure appears to be general:


R
CH2CHO
R'
CHO 0°
NaOH, 5 hrs.
80%
VIII
R
R'
CH=C-CHO
IX
1, CH3CO2Et
Na
<0°, 4 hrs.
2, warm to RT
70%
R
R'
CH=C-CH=CH-CO2Et
X


R.Ni
120°, 100 atm
autoclave
87%
R'
H
R
CH2-CH-CH2-CH2-CO2Et
R.T.
HBr
EtOH
50-60%
R'-CH-CH2CH2-CH-CH2-CH-CH2CH2CO2Et
Br
Br
R
XII
2NaCH(CO2Et)2
80%

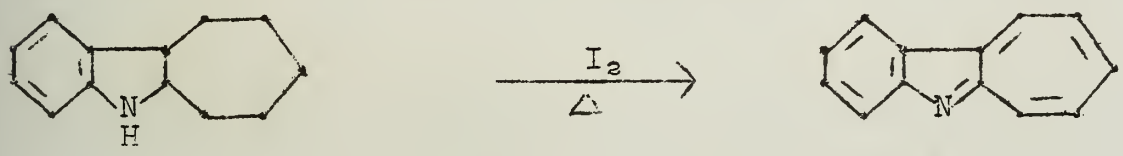

R
CH2-CH-CH2CH2CO2Et
CO2Et
CO2Et
R'
XIII
OH⊖
Δ, -CO2
97%
R
CH2-CH-CH2-CH2COOH
COOH
R'
XIV
Fe
Ba(OH)2, Δ
70-75%


R
R'
O
XV
LiAlH4
R
R'H
OH
XVI
KHSO4
Δ
R
R'
XVII
dropped on
15% Pd-C
360°, distilled.
R
R'
XVIII
R''
MgX
R
R'
R''
OH
XIX
KHSO4, Δ
R
R'
R''
XX
15%Pd-C
360°
distill
R
R'
R''
XXI

Using this general scheme, (yields based on the dehydrogenation steps XVII→XVIII and XX→XXI) Pommer synthesized azulene (VIII→XVIII; R'=R=H)(4.5%)(necessarily indicating a poor overall yield); 5-methylazulene (VIII→XVIII; R'=H, R=Me)(18%); 1,5-dimethylazulene (VIII→XVIII; R'=R=Me)(18%); 4-methylazulene (VIII→XV→XXI; R'=R=H, R"=Me)(15%); 5,8-dimethylazulene (VIII→XV→XXI; R'=H, R=R"=Me)(13%) and 5-methyl-8-isopropylazulene (VIII→XV→XXI; R'=H, R=Me, R"=isopr. (12%).

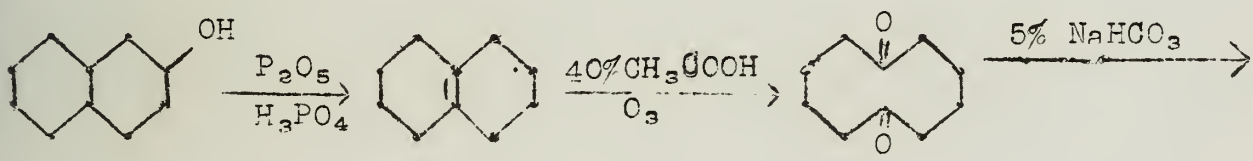
In an attempt to prepare 1,5,8-trimethylazulene through the same sequence a mixture of the 1,5,8- and 2,5,8-isomers was obtained, indicating a migration of a methyl group during or after dehydrogenation. Migrations ofan isopropyl[5] and a phenyl[11,12] group have been reported.

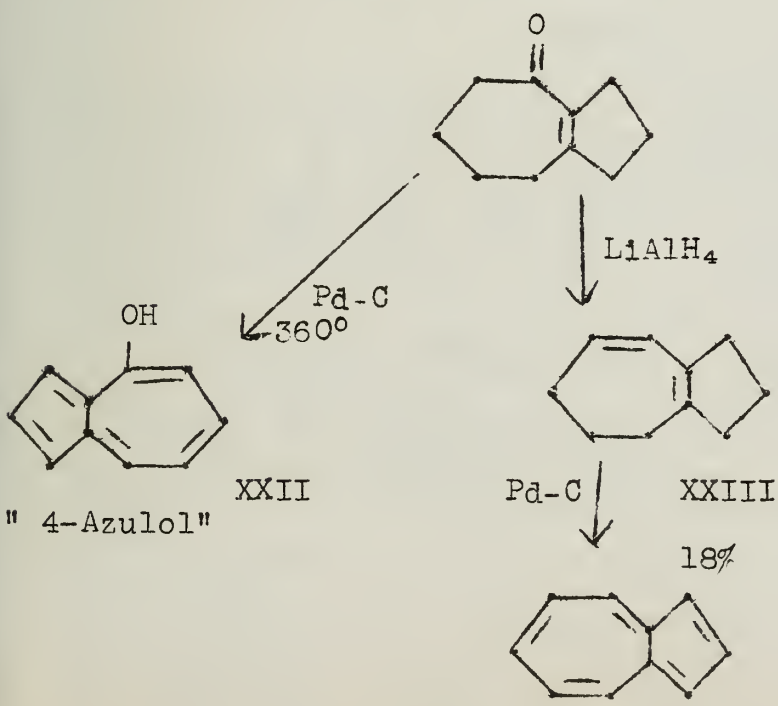
A. G. Anderson[13] reported the synthesis of what appears to be the first heteroazulene of known structure.



1-Azabenz-[b]-azulene

An improved synthesis of azulene itself not involving a ring enlargement step has been developed.[14]





XXII

" 4-Azulol"

XXIII

XXIV

Presence of the hydroxyl group in (XXII) has been demonstrated and its position inferred from the visible light absorption spectrum, which was characteristic of that given by 4-alkyl derivatives. In this regard Treibs[15] has shown that 1-methoxy and ethoxy derivatives have identical spectra with those of 1-alkyl derivatives. Bromination of (XXIII) gave three bromoazulenes of unknown structure.

Azulenes with other functional groups have been reported. Anderson has reported the preparation of 1-azuleneazobenzene from azulene and benzenediazonium chloride in the presence of sodium acetate. In acid solution a red compound is formed which gives the azo compound in brown-black needles on addition of base.[1] Treibs[16] has also reported the preparation of 6-carbethoxy-1,2-benzazuleneazobenzene by the action of phenyldiazonium chloride on 1,2-benzazulene.

Action of an excess of acetic anhydride on azulene, in the presence of aluminum trichloride and carbon disulfide, gave 1,3-diacetylazulene (62%) as red needles.[1,17]

A nitroazulene (probably the 1-nitroazulene) was obtained in red needles (51%) on treating azulene with cupric nitrate and acetic anhydride. Alkylation of azulene with methyl chloride or iodide by the Friedel-Crafts reaction gave minute quantities of 1-methylazulene (?).

In Germany synthetic azulene is being produced commercially[18]. It is being used in preparations of chamomile (which is a natural plant oil containing chamazulene) to increase the efficiency of the chamazulene present in checking skin inflammations. Other suggested uses include; addition to perfume compounds for ointments and creams, addition to therapeutic preparations, and to medicinal hair lotions, mouth washes, and tooth-pastes.

REFERENCES

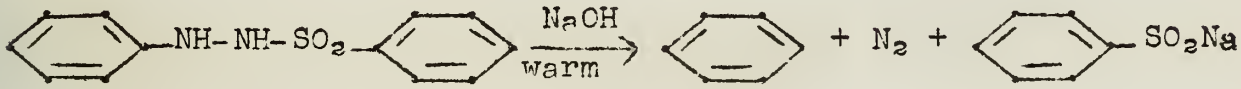
1. M. Gordon, Chem. Rev., 50, 127 (1952).
2. R. Roeske, Org. Chem. Seminars 1949-50.
3. W. Herz, J. Am. Chem. Soc., 73, 4923 (1951).
4. W. Herz, ibid., 74, 1350 (1952).
5. W. Herz, ibid., 75, 73 (1953).
6. W. Treibs, H. Barchet, G. Bach, W. Kerchhof, Ann., 574, 54 (1951).
7. W. Treibs, ibid., 574, 60 (1951).
8. Pl. A. Plattner, A. Fürst and A.R. Somerville, Helv. Chim. Acta., 34, 971 (1951).
9. H. Pommer, Naturwissenschaften, 39, 44 (1952).
10. H. Pommer, Ann., 579, 47 (1953).
11. Pl.A. Plattner, R. Sandrin, J. Wyss, Helv.Chim.Acta., 29, 1604 (1946).
12. Pl.A. Plattner, A. Fürst, M. Gordon, K. Zimmermann, ibid., 33 1910 (1950).
13. A. G. Anderson, Jr. and James Tazuma, J.Am.Chem.Soc., 74, 3455 (1952).
14. A.G. Anderson, Jr. and J. A. Nelson, ibid., 73, 232 (1951).
15. W. Treibs and A. Stein, Ann., 572, 161 (1951).
16. W. Treibs and A. Stein, ibid., 572, 165 (1951).
17. A.G. Anderson, Jr. and J.A. Nelson, J.Am.Chem.Soc., 72, 3824 (1950).
18. H. Janistyn, Perfumery and Essential Oil Record, 42, 186, 236 (1951).

ALKALINE DECOMPOSITION OF HYDRAZINE DERIVATIVES

Reported by David M. Locke April 17, 1953

Introduction

As early as 1885 the action of aqueous sodium hydroxide on benzenesulfonylphenylhydrazone was recorded by Escales.[1]



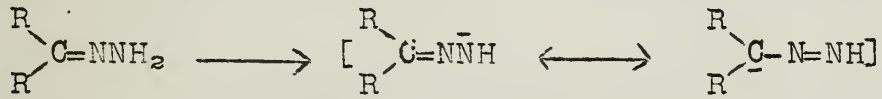
Many different types of substituted hydrazines (arylsulfonylhydrazines, hydrazides, and hydrazones) have since been reacted with basic reagents, usually at high temperatures, and their characteristic behavior under these conditions has led to the development of several useful synthetic reactions which exhibit a certain mechanistic similarity.

The Wolff-Kishner Reaction

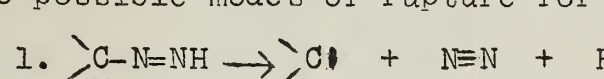
The Wolff-Kishner reaction is a well-known method for reducing a carbonyl group to a methylene group.[2] It is perhaps most conveniently used as the Huang-Minlon modification: the carbonyl compound in ethylene glycol is treated with hydrazine hydrate; after formation of the hydrazone is complete the low-boiling material is distilled off, and the hydrazone is decomposed at 200° with alkali.[3]

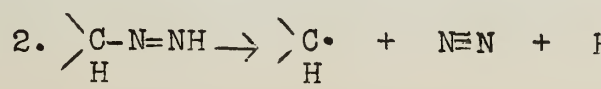
Kinetic studies by Balandin and Vaskevitch have indicated the formation of an intermediate in the reaction, and these workers have suggested the diimine, which is isomeric with the hydrazone, as the reactive intermediate.[4] Todd has suggested that the diimine then undergoes decomposition in a fashion analogous to that of dialkylazo compounds, which are known to decompose to free radicals.[5]

The base-catalysed isomerization of hydrazones to diimines has been formulated by Seibert as involving an intermediate anion.



In the Wolff-Kishner reaction this hybrid ion may itself decompose giving the observed reaction product, or it may serve only as the precursor of the diimine. In either case there are three possible modes of rupture for the C-N bond:





3. Simultaneous rupture of the C-N bond and formation of the new C-H bond.[6]

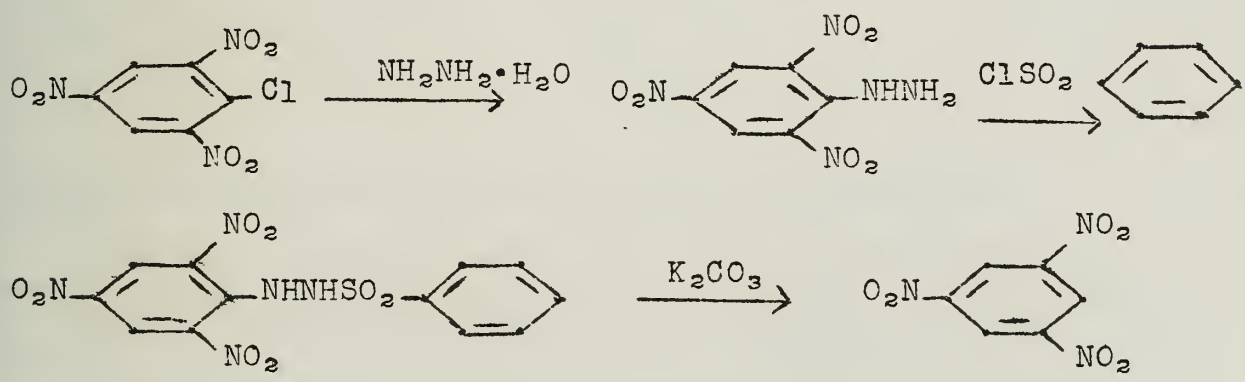
The McFadyen-Stevens Reaction

The alkaline decomposition of arylsulfonacylhydrazides has proved to be a useful method of converting acids to aldehydes. The most convenient method of preparing the arylsulfonacylhydrazide is by the action of the arylsulfonyl chloride on the acid hydrazide.[7] And it has been found that the reaction itself is best carried out with potassium carbonate in glycerol at 200°.[8] It is believed to take the following course:

The reaction fails completely with aliphatic aldehydes[7,9] and is also unsuccessful in some cases in the aromatic series. McFadyen and Stevens found that while m-nitrobenzoic acid underwent the reaction, p-nitrobenzoic acid failed to do so.[7] With carboxylic acids on heterocyclic nuclei the same sensitivity to electronic effects may be observed; picolinic and nicotinic acids, for example, react satisfactorily while isonicotinic acid does not.[10]

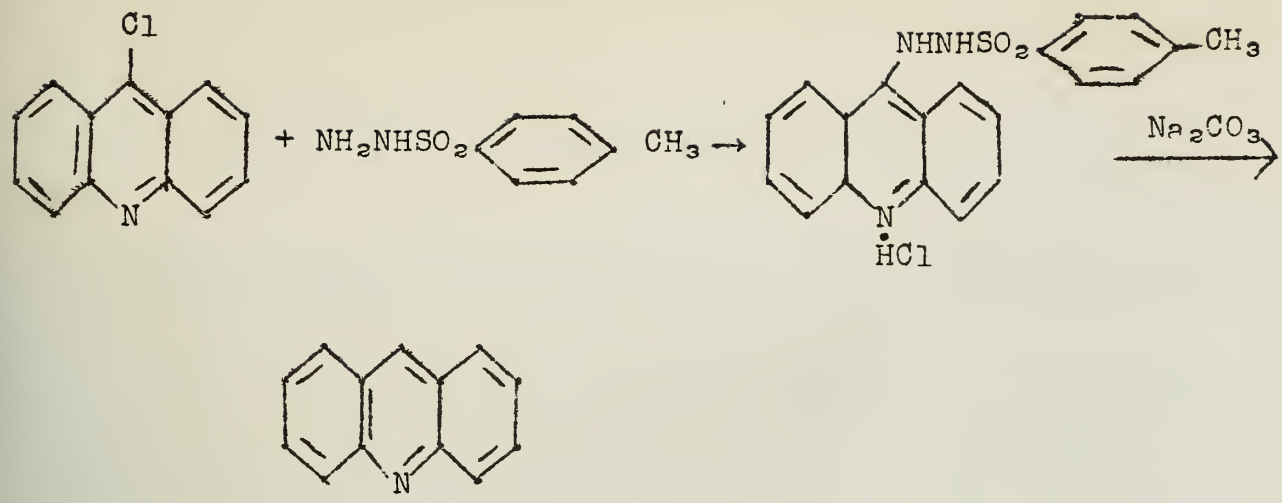
The Method of Albert and Royer

McFadyen and Stevens indicated that it was also possible to replace active halogen on the benzene ring by hydrogen in the same manner.



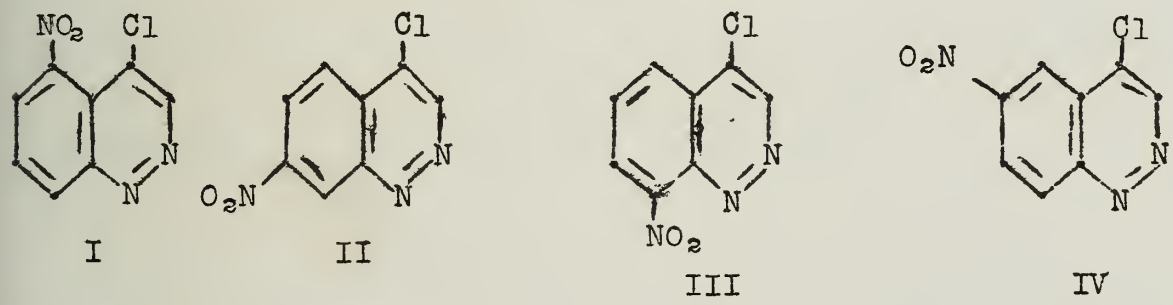
The analogy of picryl chloride with acid chlorides is well known. It is therefore, not surprising to find that it undergoes a reaction analogous to the McFadyen-Stevens reaction.

The first attempt to apply this reaction to the replacement by hydrogen of a halogen atom on a heterocyclic nucleus by Dewar met with little success.[11] An experimental procedure was, however, later worked out by Albert and Royer. It was found that sodium carbonate and ethylene glycol at temperatures above 100° performed the replacement smoothly.[12]



The reaction has since proved extremely valuable with heterocyclic compounds, particularly those containing a readily reducible group such as the nitro or cyano group. Catalytic reduction, another method of accomplishing the same conversion, cannot be used in these cases.

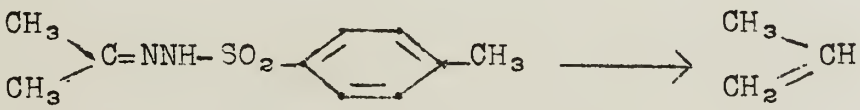
Again electronic influences are important in the reaction. For example, it was found possible to reduce by this method I, II, and III, but not IV[13]



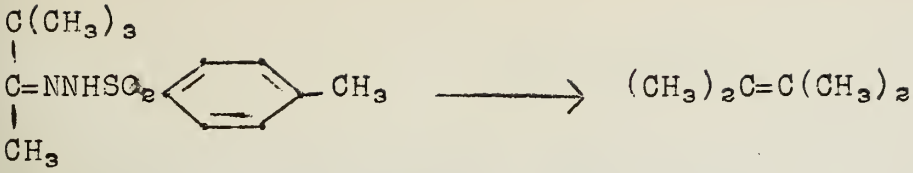
<u>Alkaline Decomposition of p-Toluenesulfonylhydrazones</u>

Bamford and Stevens have found that p-toluenesulfonylhydrazones are decomposed in a similar fashion by the action of sodium in hot ethylene glycol.[14] A variety of products was obtained, the structure of the product depending on the type of carbonyl compound used.

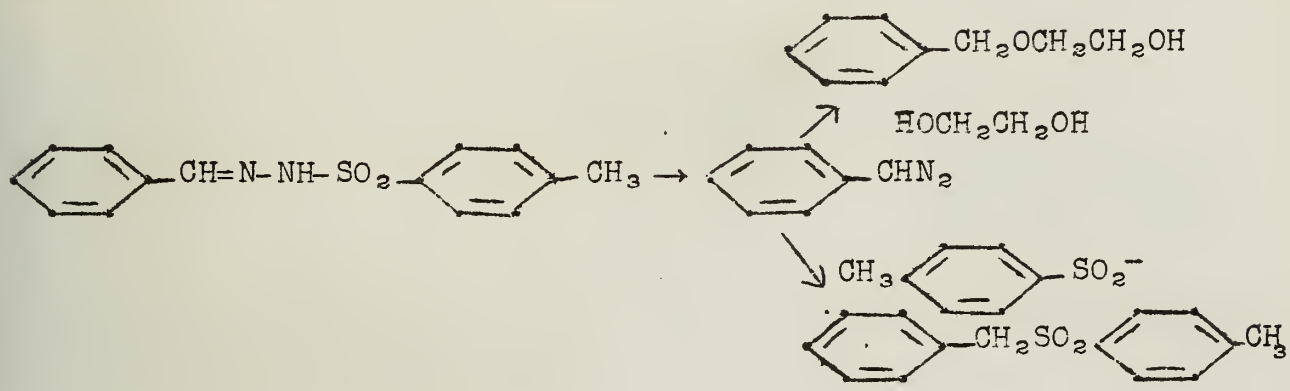
In general the p-toluenesulfonylhydrazones of aliphatic aldehydes and ketones yielded olefins.



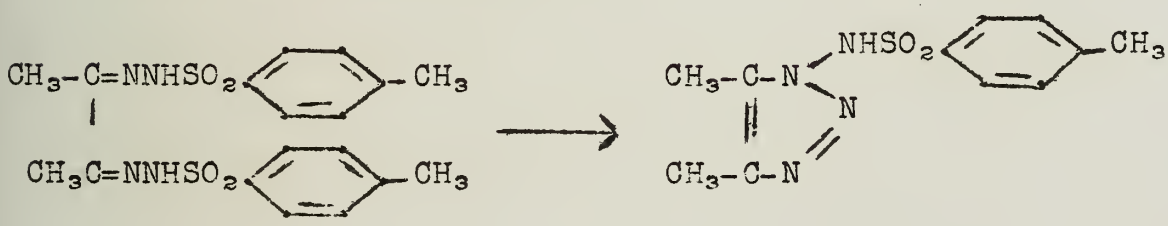
In some cases rearrangements were observed.



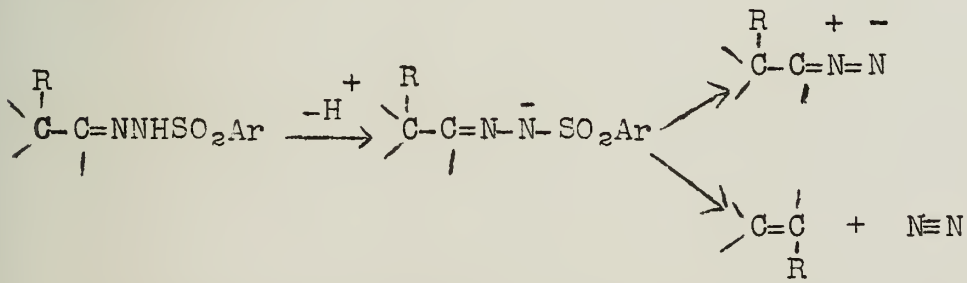
Most aromatic aldehydes and ketones gave diazo compounds or their further reaction products.



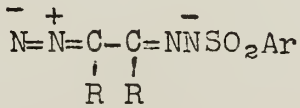
Alpha diketones were found to yield sulfonamidotriazoles.



Bamford and Stevens have outlined the following mechanism for the reaction:



The triazole from the diketone may arise from some such intermediate species as the following:



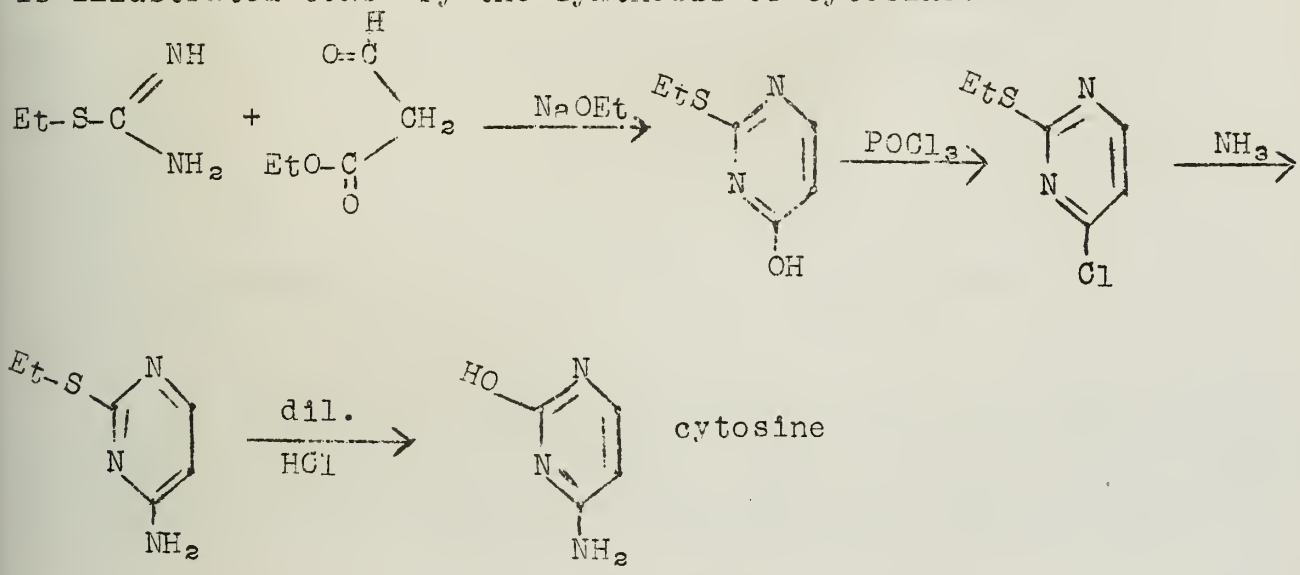
BIBLIOGRAPHY

1. Escales, Ber., 18, 893 (1885).
2. Todd, Org. Reactions, 4, 378 (1948).
3. Huang-Minlon, J. Am. Chem. Soc., 68, 2487 (1946).
4. Balandin and Vaskevich, J. Gen. Chem. (USSR), 6, 1878 (1936), [CA, 31, 4575 (1937)].
5. Todd, J. Am. Chem. Soc., 71, 1356 (1949).
6. Seibert, Ber., 80, 494 (1947), 81, 266 (1948).
7. McFadyen and Stevens, J. Chem. Soc., 1936, 584.
8. Natelson and Gottfried, J. Am. Chem. Soc., 63, 487 (1941).
9. Price, May and Pickel, J. Am. Chem. Soc., 62, 2818 (1940).
10. Niemann, Lewis and Hays, J. Am. Chem. Soc., 64, 1678 (1942).
11. Dewar, J. Chem. Soc., 1944, 619.
12. Albert and Royer, J. Chem. Soc., 1949, 1148.
13. Morley, J. Chem. Soc., 1951, 1971. Alford and Schofield, J. Chem. Soc., 1953, 609.
14. Bamford and Stevens, J. Chem. Soc., 1952, 4735.

NEW SYNTHESES OF PYRIMIDINES

Reported by Paul D. Thomas April 17, 1953

The most common method available for formation of the pyrimidine nucleus involves the base catalyzed condensation of ureas, thioureas, guanidines and amidines with active methylene compounds.[1] Most of these syntheses and others, less frequently used, yield polysubstituted pyrimidines. The substituents are often transformed into those present in the desired compound. This is illustrated below by the synthesis of cytosine.



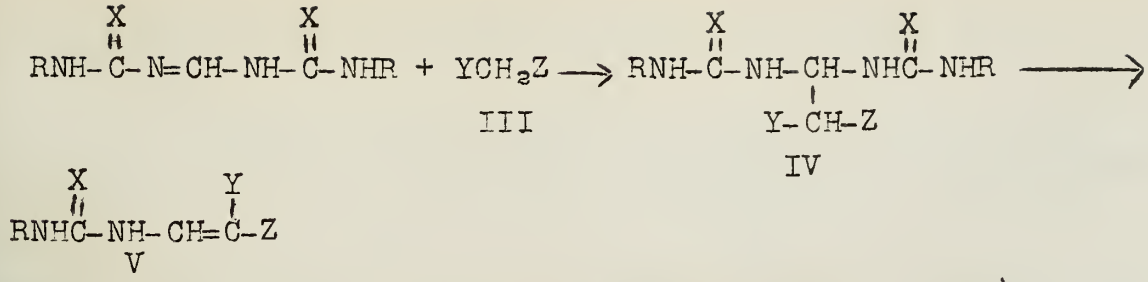
Some prominent features of pyrimidine chemistry are briefly:

(1) In simple derivatives, containing alkyl, aryl, nitro groups or halogen atoms, but no -OH or $-NH_2$ groups, the nucleus has aromatic character and behaves like that of pyridine.
(2) Nuclear substituents vary in their behavior according to the positions which they occupy. At position 5 the properties of a group can be loosely described as similar to those which it normally has when attached to an aromatic nucleus. At positions 2, 4 and 6 marked deviations from normal behavior are observed, substituents in these positions are more or less labile. The aromatic character diminishes progressively as -OH or NH_2 groups are introduced into positions 2, 4 and 6.
(3) Simple pyrimidines appear to be very resistant to electrophilic substitutions.

Very recently a new synthesis of pyrimidines, based on the condensation of orthoesters with ureas, has been developed by Whitehead.[2] This may be illustrated by the following reaction sequence:

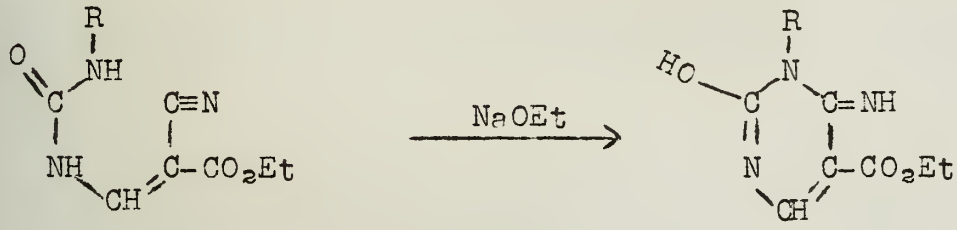
$$(1)\quad \underset{\mathrm{I}}{2\,RN{-}\overset{\overset{X}{\|}}{C}{-}NH_2} + CH(OC_2H_5)_3 \longrightarrow \underset{\mathrm{II}}{RNH{-}\overset{\overset{X}{\|}}{C}{-}N{=}CH{-}NH{-}\overset{\overset{X}{\|}}{C}{-}NHR} + 3C_2H_5OH$$

(R=H, alkyl, or aryl, X=O or R=alkyl, X=S)



(Y and Z = CN, CH_3CO, CO_2H, $CO_2C_2H_5$, $CONH_2$ or $COCO_2C_2H_5$)

(3) Cyclization of the ureidoethylenes, for example:



In the reaction of ethyl orthoformate with ureas (Equation 1) acyl ureas (I, R=CH_3CO, X=O) and N,N'-dialkyl ureas failed to react under the same conditions. Aromatic ureas (I, R-aryl, X=O) caused cleavage of the N-C bond of the urea; thus, the desired N,N'-dicarbamylformamidine (II) was not obtained as the major product.

The methylene compounds (III) undergo addition to the nitrogen-carbon double bond of the formamidines (II) producing the unstable adducts (IV) which, by loss of a molecule of the original urea, yield the ureidoethylenes (V). The rate of addition was shown to be dependent upon the activating groups Y and Z. The order of activity is $-CO_2H > -CN > -COCH_3 > -CO_2C_2H_5$. Malonic acid reacts in 3-4 minutes while malonic ester requires approximately 60 hours.

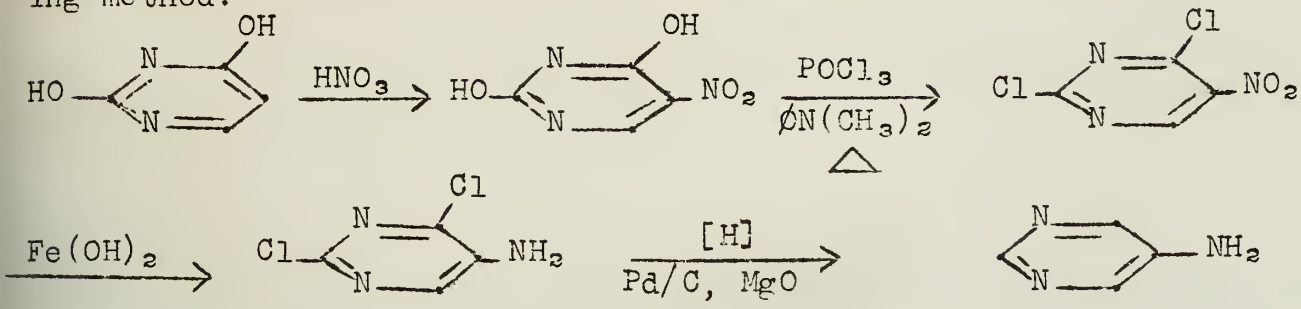
Whitehead[3] was also able to obtain the ureidoethylene intermediates (V, R=alkyl, X=O, Y=Z=$CO_2C_2H_5$) by the reaction of ureas with diethylethoxymethylenemalonate. These intermediates could be cyclized to 5-carbethoxyuracils, the amides of which showed diuretic activity.

Simple Pyrimidines

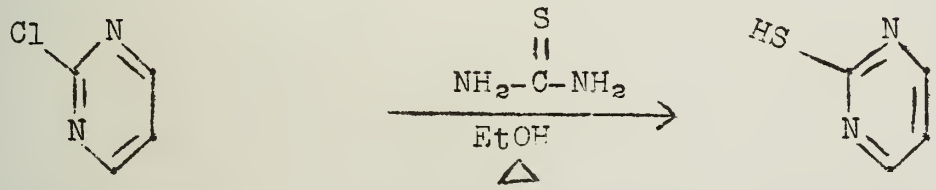
Recent attempts have been made to correlate the structure of polysubstituted pyrimidines with their infrared[4] and ultraviolet[5] absorption spectra, but these attempts have been handicapped by the lack of suitable model compounds. Several English workers[6-12] have undertaken the preparation of monosubstituted pyrimidines for fundamental physical, chemical and biological studies; as a result, new pyrimidines have been reported, and some older syntheses improved.

In order to prepare the parent compound, Whittaker[12] has reported 92% yields of pyrimidine by use of palladium-charcoal with MgO on 2-chloropyrimidine. Other less successful methods are also reported.

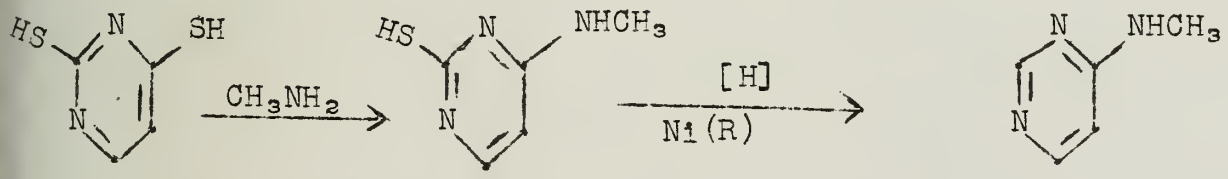
5-aminopyrimidine has been prepared from uracil by the following method:[12]



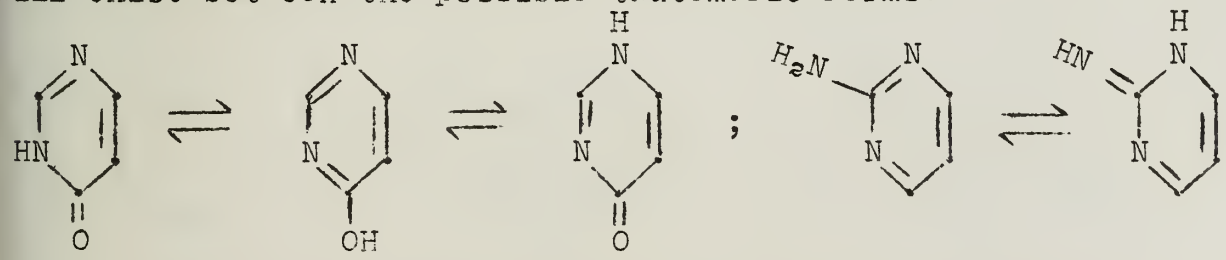
A new synthesis of mercaptopyrimidines[6,8] is illustrated by the example below:



The yields are from 50-90%, and with the monochloro compounds no intermediate products were isolated. This method is also successful with dichloropyrimidines, it was not successful with the corresponding bromo derivatives. This is a considerable improvement, in many cases, over the previous methods. The mercapto compounds are useful intermediates for obtaining other pyrimidines, for example:



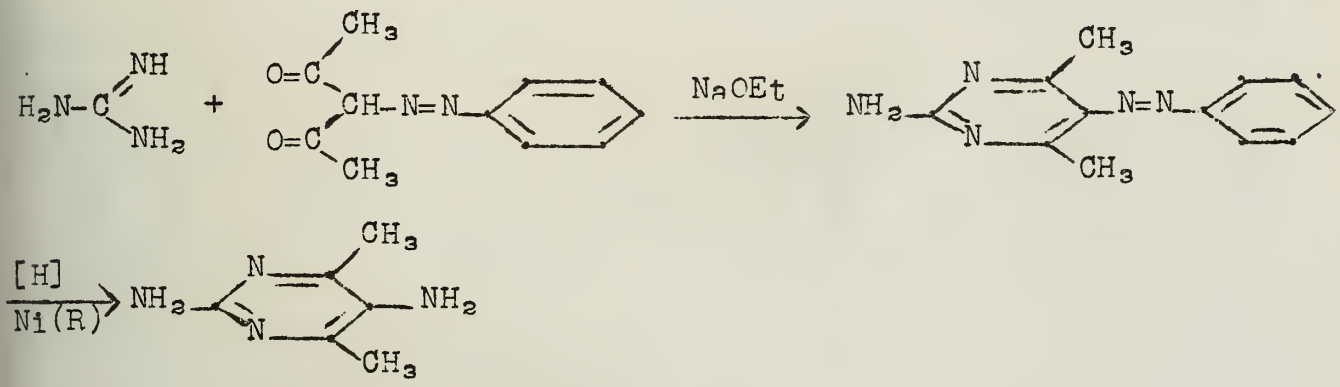
In considering the structure of hydroxy; mercapto or aminopyrimidines, it is important to note that in solution an equilibrium will exist between the possible tautomeric forms.



By comparison of the ultraviolet and infrared spectra of the hydroxypyrimidines with those of the corresponding methoxy derivatives it has been shown that 4-hydroxypyrimidine[11] and 2-hydroxypyrimidine[6] exist mainly in the lactam forms in aqueous solution. Similar comparison of aminopyrimidines and the corresponding dimethylamimo compounds have shown that the amino form is predominant.

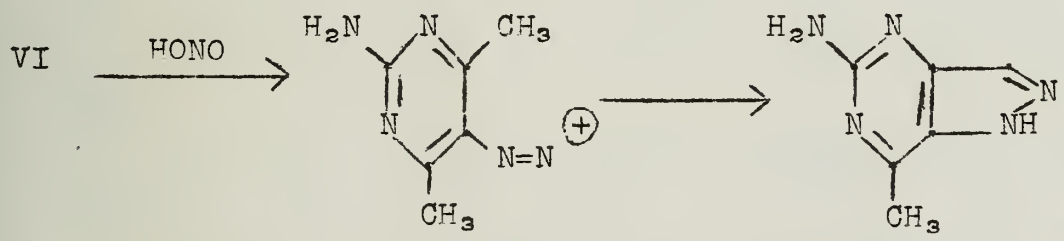
New snytheses based on 5-aminopyrimidines.

Todd[15,16] has earlier shown that condensation of guanidines with azo-1,3-dicarbonyl compounds followed by catalytic reduction of the resulting intermediate 5-azopyrimidines is a useful route to polysubstituted 5-aminopyrimidines.

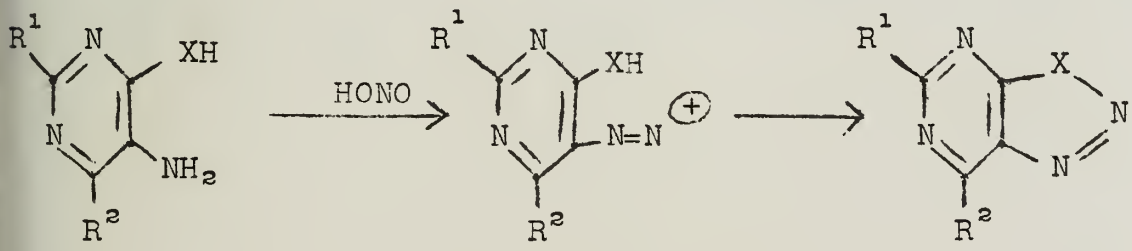


VI

This work has been extended by Rose.[17] The properties of the pyrimidine VI were studied. It was shown to be freely water soluble and its solutions exhibited strong fluorescence. Acetylation and benzoylation give the 5-acyl derivatives. These did not react with nitrous acid. The 5-amino compound could be diazotized to form a rather stable diazonium salt which could be easily cyclized in good yield to the corresponding tetraazaindene.



This prompted a study of other 5-aminopyrimidines of the type VII in this reaction.

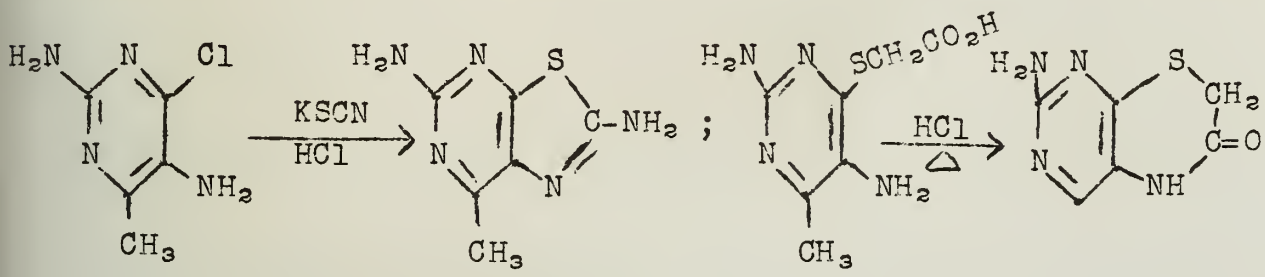


VII VIII IX

The nature of the substituent X markedly influenced the ease of formation of the pyrazole ring. With X=NH, RN, O or S the diazonium salt cyclized preferentially to give triazole, oxadiazole and thiadiazole rings respectively. Compounds of the type IX were

successfully prepared directly from diazotized VII when R^2 was alkyl, phenyl, dialkylamino, alkylthio and carboxymethylthio. The substituents R^1 were NH_2-, CH_3S-, CH_3NH-, $(CH_3)_2N$-, EtNH-, nC_3H_7NH-, iC_3H_7NH-, nC_4H_9NH-, iC_4H_9NH-, $nC_5H_{11}NH$-, piperidino-, guanidino, p-chlorophenylguanidino and p-anisidino. Yields in some instances were low.

Other heterobicyclic systems were prepared from compounds of the type VII as shown below.



BIBLIOGRAPHY

1. B. Lythgoe, Quart. Revs., 3, 181 (1949).
2. C. W. Whitehead, J.A.C.S., 75, 671 (1953).
3. C. W. Whitehead, ibid., 74, 4267 (1952).
4. I. A. Brownlie, J. Chem. Soc., 3062 (1950).
5. L. F. Cavalieri and A. Bendich, J.A.C.S., 72, 2587 (1950).
6. M. P. V. Boarland and J. F. W. McOmie, J. Chem. Soc., 1218 (1951).
7. M. P. V. Boarland and J. F. W. McOmie, ibid., 3716 (1952).
8. M. P. V. Boarland and J. F. W. McOmie, ibid., 3722 (1952).
9. M. P. V. Boarland, J. F. W. McOmie and R. N. Timms, ibid., 4691 (1952).
10. M. P. V. Boarland and J. F. W. McOmie, ibid., 4942 (1952).
11. D. J. Brown and L. N. Short, ibid., 331 (1953).
12. N. Wittaker, ibid., 1565 (1951).
13. J. Braddiley, B. Lythgoe and A. R. Todd, ibid., 571 (1943).
14. J. R. Marshall and J. Walker, ibid., 1004 (1951).
15. R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman and A. R. Todd, ibid., 357 (1946).
16. R. Hull, B. J. Lovell, H. T. Openshaw and A. R. Todd, ibid., 41 (1947).
17. F. L. Rose, ibid., 3448 (1952).

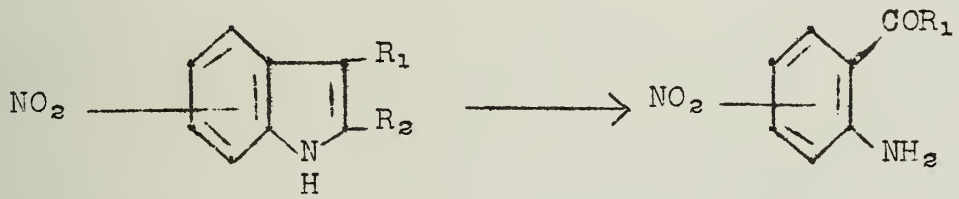
OXIDATION OF INDOLES

Reported by Allan S. Hay April 24, 1953

In 1881 Jackson[1] treated 2-methylindole with alkaline permanganate and by oxidative fission of the 2,3-double bond, acetylanthranilic acid was obtained. The same product was obtained

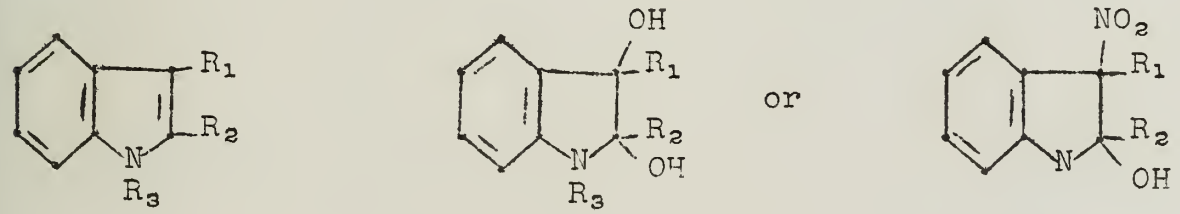
by Baudisch and Hoschek[2] in 1916 by autoxidation of 2-methylindole in the presence of sunlight.

More recently interest has been revived in this type of reaction because it has provided routes to various 2-aminoaryl ketones. Chromic acid in glacial acetic acid has commonly been used, notably by Schofield[3] and his coworkers. Excellent yields were obtained by oxidation of some nitro-2,3-diphenylindoles to the corresponding benzophenones ($R_1 = R_2 = \phi$). When the substituent in the 2-position (R_2 = alkyl) is alkyl good yields may



also be obtained, however, when both groups are alkyl ($R_1 = R_2$ = alkyl) vigorous oxidation occurs resulting in appreciably lower yields.

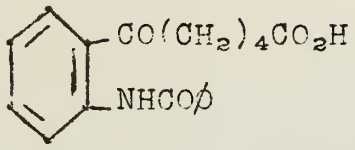
Nitration with mixed acids of 2,3-dialkylindoles yields the expected 5-nitroindoles. However, when the indole nitrogen is acylated, different results are obtained[4]. For example, with



I II

tetrahydrocarbazole ($R_1 + R_2 = -(CH_2)_4-$) when R_3 is acetyl, carbethoxyl or phenylacetyl, a product of type I is obtained. When R_3 is benzoyl, type II is obtained which may be converted to type I by boiling in ethanol. By boiling II in aqueous potassium

hydroxide the 2,3 bond may be broken to give III.

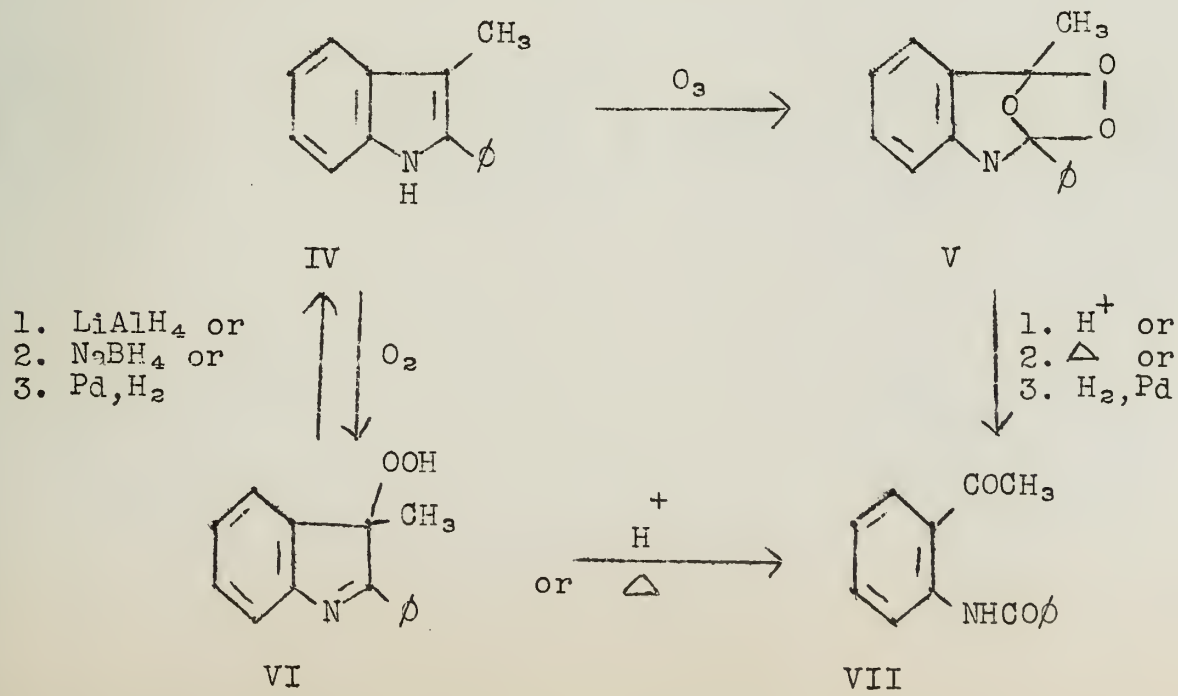


III

Glycols of type I have more recently been obtained by oxidation with osmium tetroxide[5]. The N-acetyl derivatives of tetrahydrocarbazole, and 2,3-dimethyl-,2,3-diphenyl-, and 2,3,5-trimethylindole with osmium tetroxide in pyridine - benzene gave, quantitatively, highly crystalline osmic esters, which were hydrolyzed to the glycols in moderate yield. Crystalline products were in no case obtained from N-unsubstituted indoles; in such experiments colloidal osmium was liberated.

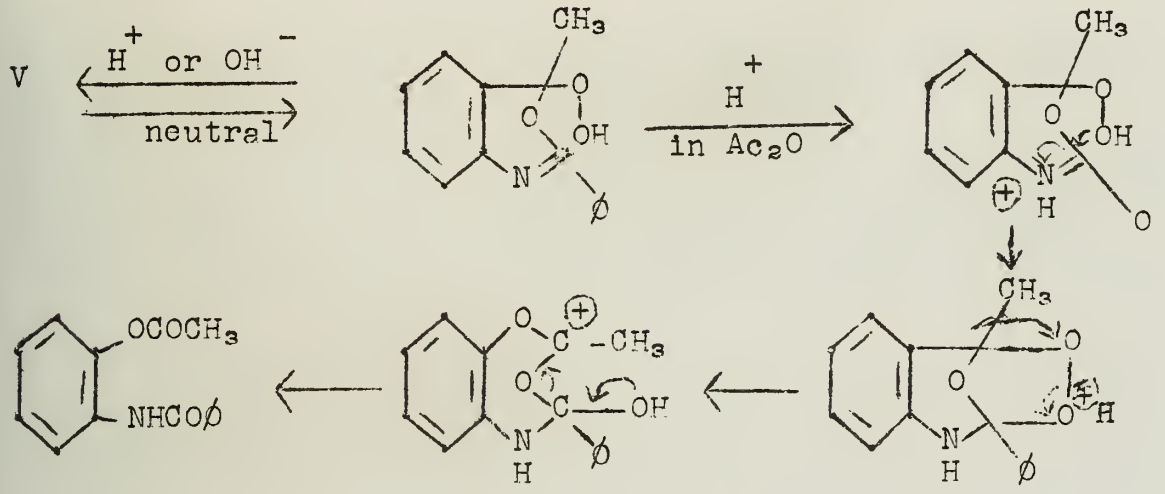
Ozone has been used by various authors for oxidative fission of the 2,3-double bond. Schofield et al[5] have treated a number of indoles with this reagent in various solvents. The yields of ketones obtained range from zero to about sixty per cent, surpassing those from chromic acid oxidation only when indoles with alkyl groups in the 2-, and 3-positions are oxidized.

In some instances the isolation of relatively stable, crystalline ozonides has been reported. Witkop and Patrick[6] have studied extensively the ozonide (V) obtained from phenylskatole (IV). It is unusually stable and may be recrystallized from boiling ethanol and stored in any quantity. Molecular weight determinations have shown that it is a monomer. Benzoylaminoacetophenone (VII) is obtained from it by treatment with acid, heat, or hydrogenation with palladium in ethyl acetate[7].



The hydroperoxide (VI) obtained from phenylskatole by autoxidation in hydrocarbon solvents undergoes an acid - catalyzed rearrangement to give the same product[6].

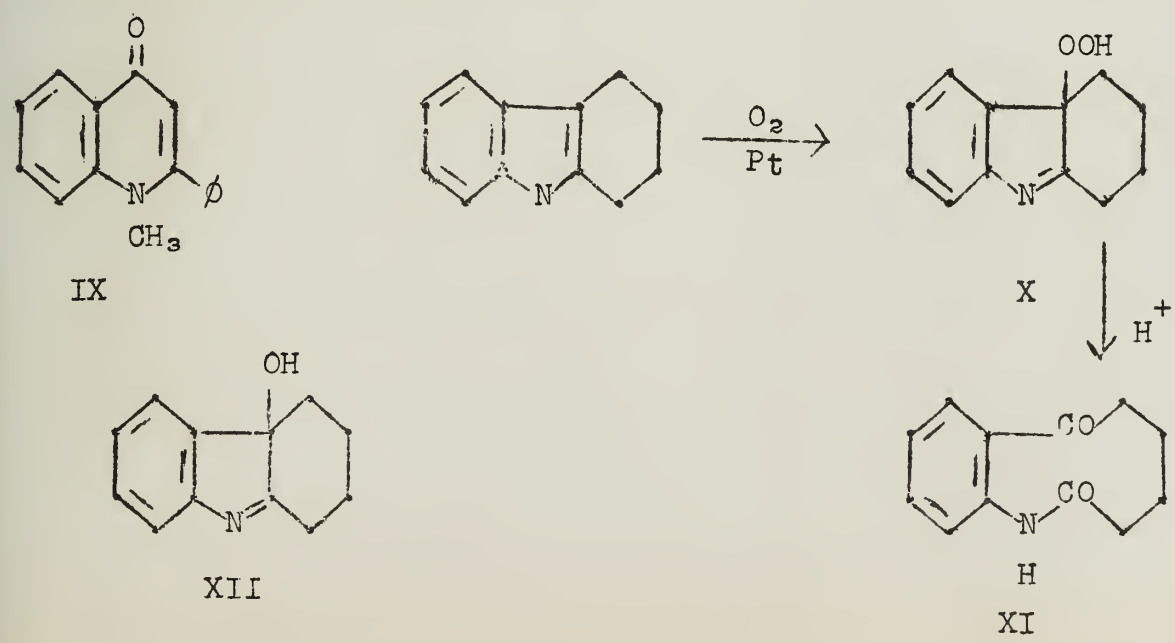
Ozonides of this type have been formulated as ring-chain tautomers[6] by Criegee. Treatment of the crystalline sulfate of the ozonide (V) with acetic anhydride gives N-benzoyl-O-acetyl-o-aminophenol (VIII). The following mechanism has been put forth.



VIII

By the reaction of the ozonide with metallic potassium in boiling benzene and subsequent methylation, 1-methyl-2-phenyl-4-quinolone (IX) was obtained[6].

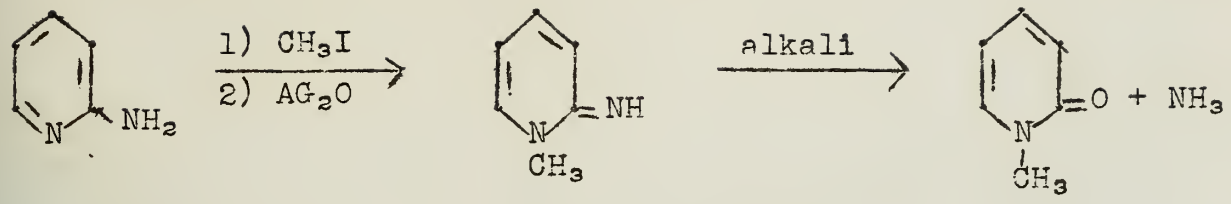
The catalytic oxidation of tetrahydrocarbazole with platinum catalyst and oxygen has been studied recently[8]. The hydroperoxide (X) obtained is fairly stable in the dry state but changes rapidly in the presence of polar solvents to the cyclic lactam(XI).

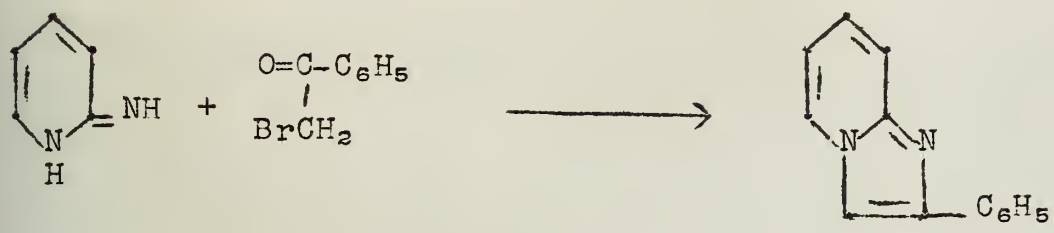


The same lactam is obtained in excellent yield from tetrahydrocarbazole by treatment with ozone in methanol at -79°, or by oxidation of 11-hydroxy-tetrahydrocarbazolenine (XII) with perbenzoic acid[8].

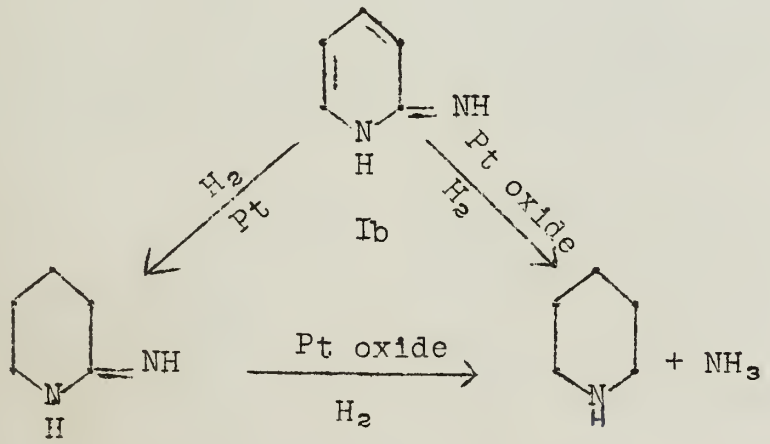
BIBLIOGRAPHY

1. O. R. Jackson, Ber. 14, 885 (1881).
2. O. Baudisch and A. B. Hoschek, ibid., 49, 2579 (1916).
3. K. Schofield and R. S. Theobald, J. Chem. Soc., 1505 (1950).
4. K. Schofield, Quart. Rev., 4, 391 (1950).
5. D. W. OcKenden and K. Schofield, J. Chem. Soc., 612 (1953).
6. B. Witkop and J. B. Patrick, J. Am. Chem. Soc., 74, 3855 (1952
7. B. Witkop and J. B. Patrick, ibid., 74, 3861 (1952).
8. B. Witkop and J. B. Patrick, ibid., 73, 2197 (1951).





(3) Behavior on catalytic reduction. Reduction of 3-aminopyridine with platinum oxide as a catalyst yields 3-aminopiperidine.[9] However, the reduction of the 2-isomer has been reported to proceed differently upon reduction with either platinum or platinum oxide.[10] The reduction of (I) with platinum as a catalyst gave a quantitative yield of 2-iminopiperidine while reduction with platinum oxide as a catalyst gave piperidine. Attempts to prepare 2-aminopiperidine from 2-iminopiperidine by hydrogenation with a platinum oxide catalyst were unsuccessful; only starting material and piperidine could be isolated. This behavior has been explained by assuming the existence of 2-aminopyridine in the imino form (Ib).



EVIDENCE FOR THE AMINO FORMS.

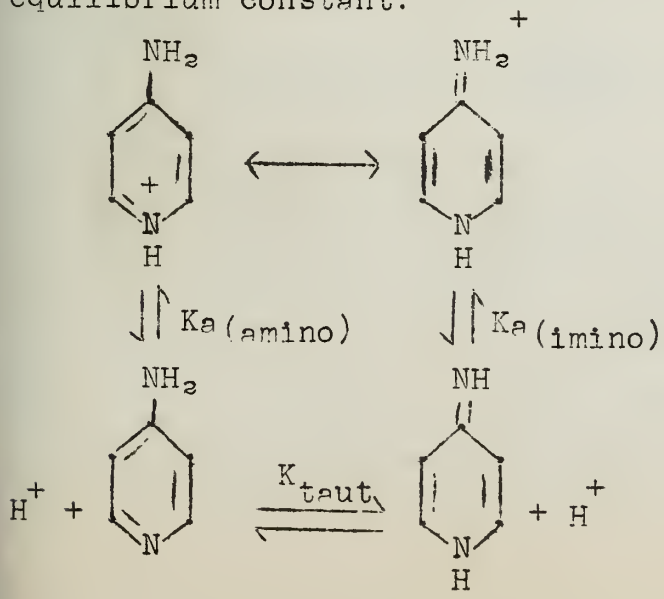
((I) Resonance energy. It has been well established that 2- and 4-hydroxypyridine exist mainly in the pyridone form.[11] From this fact an analogy has been drawn between the hydroxypyridines and their amino counterparts. This analogy is not as well grounded as it may appear. In the tautomeric equilibrium $-NH-C=O \rightleftharpoons -N=C-OH$,

the former tautomer is more stable by about 10 kcal/mole.[15] Thus, any energy gained from resonance contributions due to the enol form is counterbalanced by the gain in bond energy of the keto form, and the keto form might well be expected to predominate. On the other hand, in the amidine system $-NH-C=NH \rightleftharpoons -N=C-NH_2$ there is no change in bond energies[15] and , therefore, there is nothing to compensate for the loss in resonance energy resulting from a change from the aromatic amino to the non-aromatic imino form. The aminopyridines should, therefore, be expected to exist in the amino form.

(2) Absorption spectra. A study has been made of the ultraviolet absorption of the aminopyridines and some of their derivatives.[13,14] The spectra of 1-methyl-2-pyridone-imine (III), 2-(dimethylamino)-pyridine (V) (definitely in the amino form), and 2-aminopyridine (I) were obtained and compared. The spectrum of 2-aminopyridine (I) corresponded to that of (V) and not to that of (III), thus, indicating that (I) is in the amino form (Ia). The spectra of 1-methyl-4-pyridone-imine (VI), 4-(dimethylamino)-pyridine (VII), and 4-aminopyridine (II) produced the same results. No evidence was obtained for the presence of the imino forms (Ib) and IIb).

The infra-red spectra of the aminopyridines and some related compounds were obtained and compared.[14,16] The spectra of 2- and 4-aminopyridine closely resembled those of aniline, p-nitroaniline, α-naphthylamine, and 3-aminopyridine. On the other hand, the spectra of 2- and 4-aminopyridine differed from the spectra of 1-methyl-2-pyridone-imine (III) and 1-methyl-4-pyridone-imine (VI) respectively. These studies indicate that 2- and 4-aminopyridine exist in the amino forms rather than in the imino forms.

(3) Determination of the tautomeric equilibrium constant[1]. Since, by the addition of a proton, the same resonating cation is obtained from both the amino and the imino forms, the following equilibria coexist, where K_a(amino) and K_a(imino) are the acid dissociation constants of the cation as the conjugate acid of the amino and imino forms respectively, and K_{taut} is the tautomeric equilibrium constant:



$$K_a(\text{amino}) = [\text{amino}][H^+]/[\text{cation}]$$

$$K_a(\text{imino}) = [\text{imino}][H^+]/[\text{cation}]$$

$$K_{taut} = [\text{amino}] / [\text{imino}] = K_a(\text{amino})/K_a(\text{imino})$$

The difficulty of determining the dissociation constants of both of the tautomers limits the applicability of this procedure. However, significant results have been obtained by the use of appropriate approximations. The Ka of the corresponding 1-methyl pyridone-imine (Ka(Me)) was substituted for Ka(imino). Likewise, the Ka of the aminopyridines themselves was substituted for Ka(amino) with the assumption that the concentration of the imino form is very small in comparison with the concentration of the amino form.

	$_pKa$	$_pKa(Me)$	K_{taut}	ΔF (kcal/mole)
2-aminopyridine	6.86	12.20	$2x10^5$	7.3
4-aminopyridine	9.17	12.5	$2x10^3$	4.5

The large values for K_{taut} obtained in the experiment indicates that the predominant species present in both 2- and 4-aminopyridine is the amino form rather than the imino form.

The validity of the calculations holds only for the dilute aqueous solutions in which the $_pKa$ values were determined. On the other hand, the large ΔF values indicate that a change in solvent is not likely to change the position of the equilibrium.

CONCLUSION.

The data presented support the assignment of the amino rather than the imino structure to the 2- and 4-aminopyridines.

BIBLIOGRAPHY

1. S. J. Angyal and C. L. Angyal, J. Chem. Soc., 1461 (1952).
2. W. Marckwald, Ber., 27, 1317 (1894).
3. L. C. Craig, J. Am. Chem. Soc., 56, 231 (1934).
4. N. V. Sidgwick, The Organic Chemistry of Nitrogen, Rev. by T. W. J. Taylor and W. Baker, Oxford, 1942, p. 529.
5. A. E. Tschitschibabin, R. A. Konowalowa, Ber., 54, 814 (1921).
6. A. E. Tschitschibabin and E. D. Ossetrowa, ibid., 58, 1708 (1 (1925).
7. A. E. Tschitschibabin, ibid., 59B, 2048 (1926).
8. A. E. Tschitschibabin and M. Plaschenkowa, ibid., 64, 2842 (1931).
9. H. Nienburg, ibid., 70B, 635 (1935).
10. T. B. Grave, J. Am. Chem. Soc., 46, 1460 (1924).
11. R. C. Elderfield, Heterocyclic Compounds, I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 435.
12. R. C. Elderfield, ibid., p. 444.
13. L. C. Anderson and N. V. Seeger, J. Am. Chem. Soc., 71, 340 (1949).
14. J. D. S. Goulden, J. Chem. Soc., 2939 (1952).
15. G. E. K. Branch and M. Calvin, The Theory of Organic Chemistry, Prentice-Hall, Inc., New York, N. Y., 1941, p. 289.
16. C. L. Angyal and R. L. Werner, J. Chem. Soc., 2911 (1952).

REACTIONS OF 1,1-DIARYLETHYLENES

Reported by Robert J. Lokken April 24, 1953

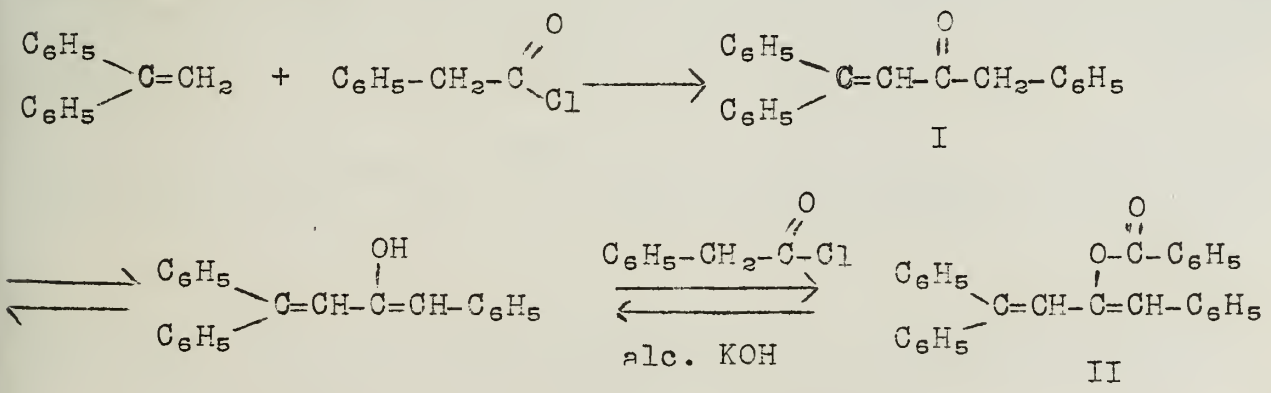
Introduction

Some interesting reactions of 1,1-diarylethylenes have been observed in which the ethylenic double bond behaves not as an aliphatic, but as an aromatic double bond. These compounds react with acid chlorides and with thionyl chloride in a manner analogous to that of Friedel-Crafts reactions with the exception that no Friedel-Crafts catalyst is employed. As in the Friedel-Crafts reaction, substitution rather than addition to the double bond takes place.

Reaction with Acid Chlorides

Recently, Bergmann has investigated the reaction of 1,1-diarylethylenes with acyl chlorides in the absence of a Friedel-Crafts catalyst. Aluminum chloride could not be used because it promotes dimerization and nuclear acylation. However, since aromatic hydrocarbons have been acylated at high temperatures without a catalyst,[6] it is not too much to expect that these ethylenic double bonds, which are so susceptible to polarization, could be acylated in the absence of a catalyst.

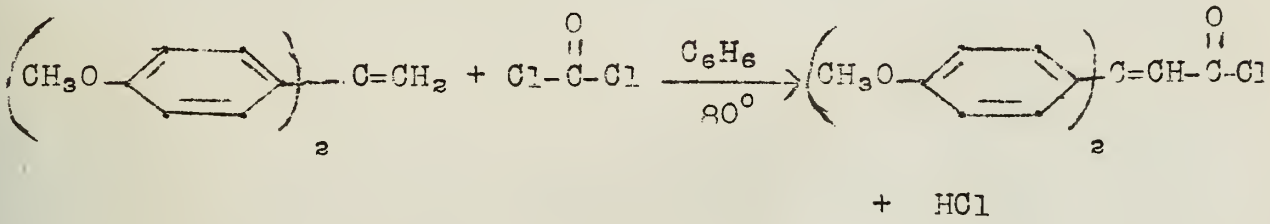
Indeed, Bergmann found that 1,1-diphenylethylene was acylated by benzoyl-, cinnamoyl-, and fumaryl chlorides to give the corresponding ketones, fumaryl chloride reacting with only one mole of olefin. When phenacetyl chloride was used, what at first appeared to be a different reaction occurred. Two moles of acid chloride were used per mole of olefin and the product was not the expected ketone (I). However, treatment with alcoholic potassium hydroxide converted the product to (I). Since the ultra-violet absorption spectrum of the original product resembled very closely that of 1,1,4-triphenyl butadiene, Bergmann decided that the reaction proceeded as expected to give the ketone (I), but that the enol form of the ketone was benzoylated to give the product (II) which was isolated.



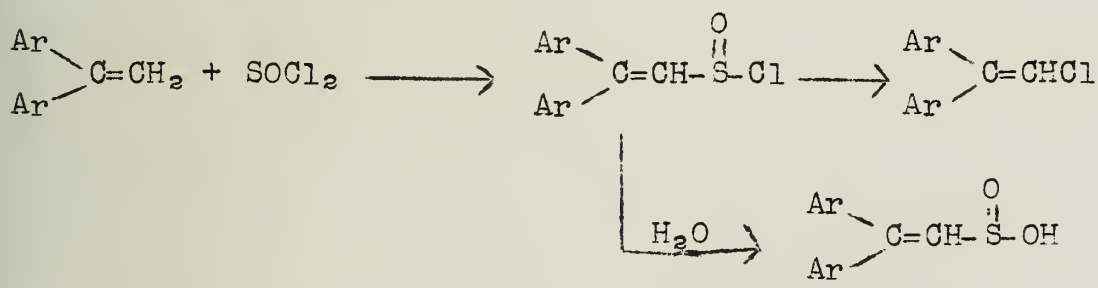
Of several saturated aliphatic acyl chlorides which were tried, none reacted with 1,1-diarylethylenes because they decomposed at a temperature below that necessary to promote this type of reaction (190-200°).

Reaction with Thionyl Chloride

1,1-Dianisylethylene, according to Patai and Bergmann, is so active that it reacts with phosgene to produce the corresponding acid chlordie and hydrochloric acid.[1,7]

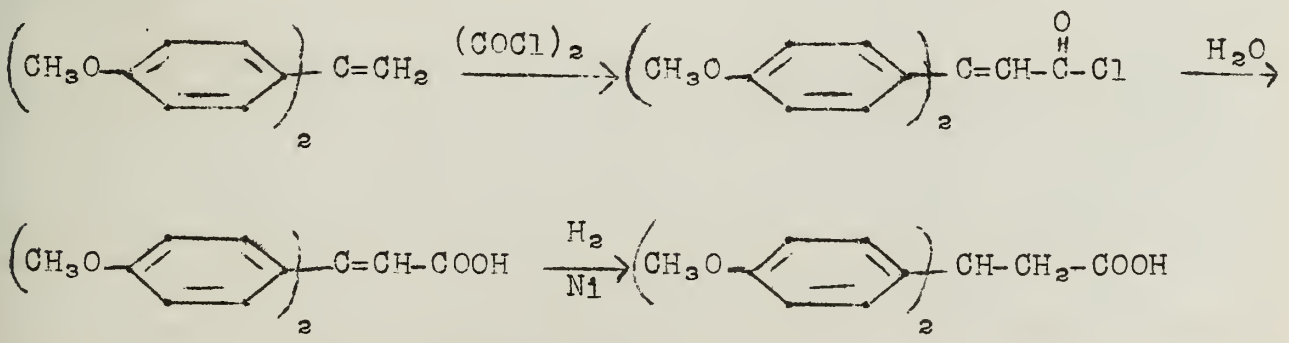


Following this observation they experimented with thionyl chloride, a formal analog of phosgene, in the hope that it too might react with diarylethylenes. On treating the reaction mixtures with water, they obtained the sulfinic acids corresponding to the diarylethylenes which were used. However, the major product was the diarylvinyl chloride, which could be formed from the sulfinyl chloride by loss of sulfur monoxide. This is the most convenient method for making diarylvinyl halides.



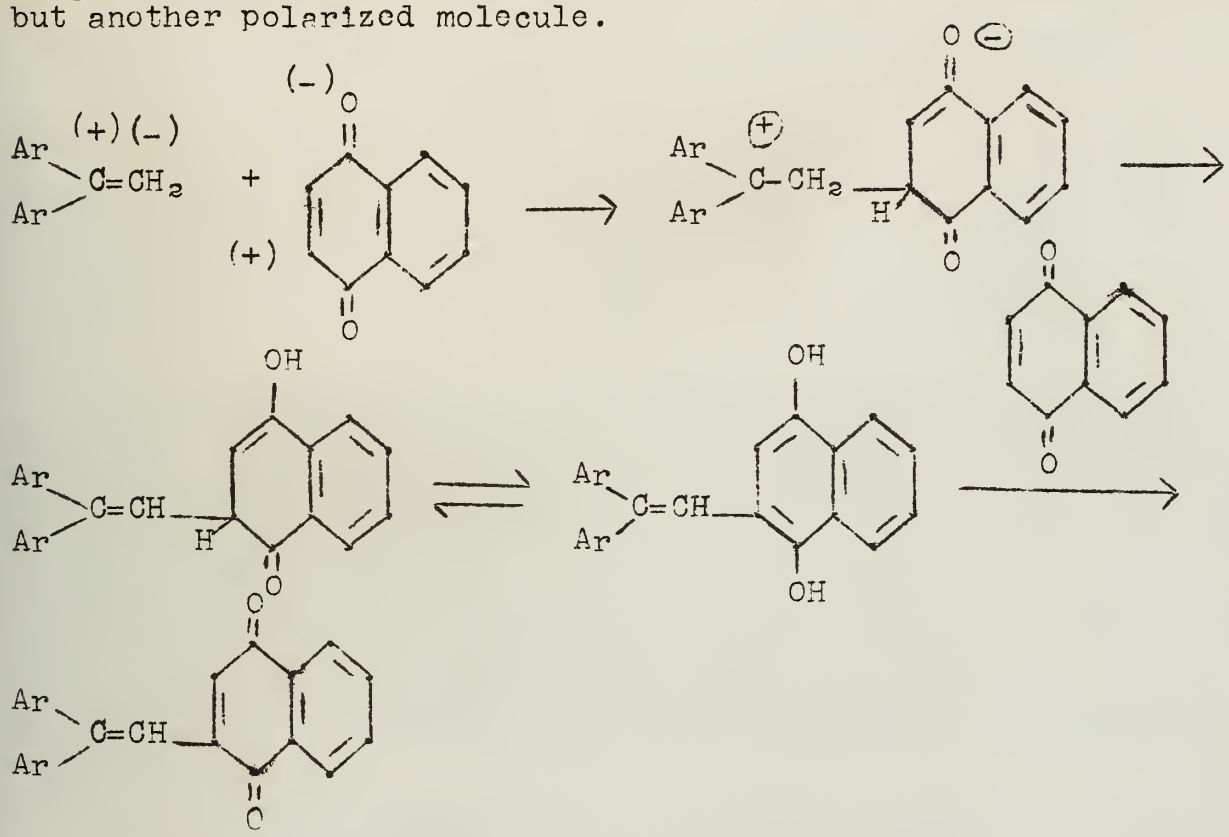
Reaction with Oxalyl Chloride

The reaction of 1,1-diarylethylenes with oxalyl chloride is probably the most attractive of all from a synthetic point of view. The primary product is a β,β-disubstituted acrylyl chloride, which can be hydrolyzed to the acid, which can in turn be hydrogenated catalytically to the β,β-disubstituted propionic acid.



Reaction with Quinones

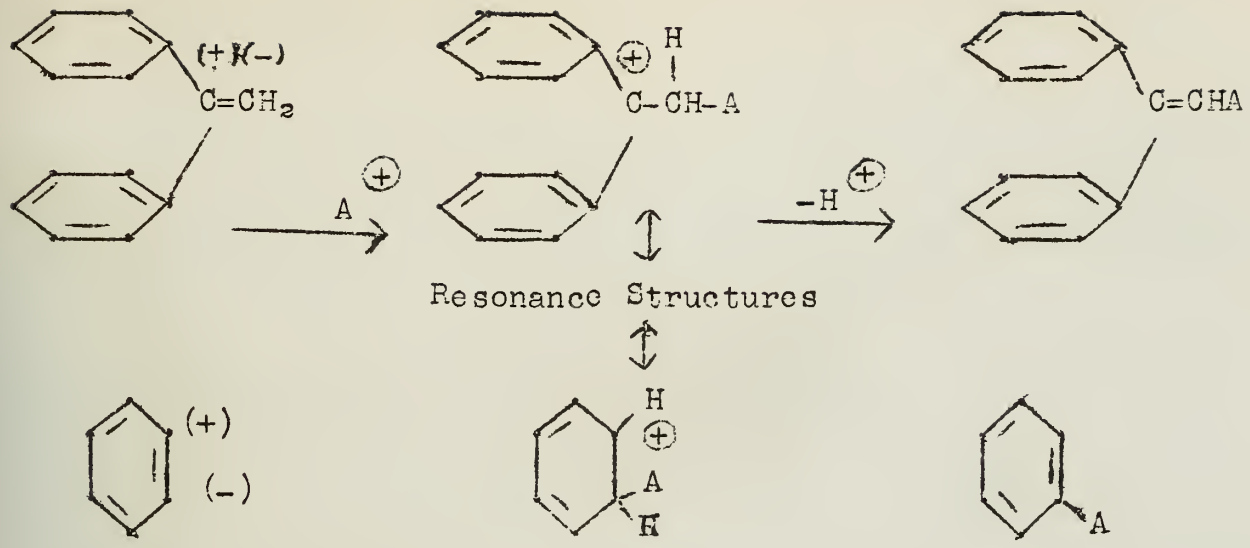
The condensation of quinones with 1,1-diarylethylenes has been studied by Gates. The mechanism of the reaction is essentially the same as that of the other reactions discussed. There is a slight difference in that the attacking species is not an ion, but another polarized molecule.



Apparently this type of condensation is not as facile as that of acid chlorides with diarylethylenes. For the quinone condensations, compounds with strong electron-donating groups on the aromatic nuclei are necessary. For example, 1,1-dianisylethylene condensed with α- naphthoquinone but not with β -naphthoquinone, while 1,1-bis-(p-dimethylaminophenyl)-ethylene reacted readily with both α - and β - naphthoquinone.

Mechanism

The surprisingly high degree of aromaticity of the ethylenic double bond is due to its conjugation with the aromatic nuclei. At the approach of a polar reagent, $A^{\oplus}$, polarization of the double bond is enhanced because the positive charge which is developed on the 1-carbon atom can be dispersed over the two aromatic rings. The reagent attacks the center of induced negative charge, and the resulting highly resonance-stabilized carbonium ion can then lose a proton to form the substituted diarylethylene. This mechanism is exactly analogous to that of aromatic substitution, as is shown in the following scheme:



There is much experimental evidence to substantiate the proposal of an ionic rather than a free radical mechanism for these reactions. For example, Kharasch has found that the reactions of oxalyl chloride with unsaturated hydrocarbons are neither catalyzed by free radical catalysts such as light and peroxides nor inhibited by free radical inhibitors. Kharasch has found further that compounds which readily add reagents of the type HX by a polar mechanism react with oxalyl chloride, while others do not.[5] Gates has proposed that the driving force behind the reactions of quinones with 1,1-diarylethylenes is the electron deficiency of the quinone and the electron-donating power of the polarized ethylene molecule.[4]

The effect of substituents on the aryl nuclei also supports the ionic mechanism. It has been found that electron-donating substituents increase the rate of reaction, while electron-withdrawing groups decrease it.[1] This would be expected in view of an ionic mechanism, because the more negative aryl nuclei would be better able to distribute positive charge.

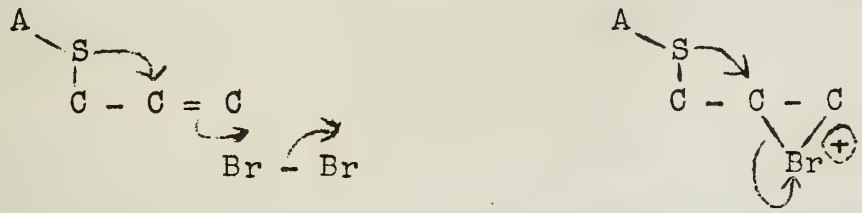
BIBLIOGRAPHY

1. Bergmann, et al, J. Am. Chem. Soc., 70, 1612 (1948).
2. Bergmann, J. Chem. Soc., 1952, 2522.
3. Gates, J. Am. Chem. Soc., 66, 124 (1944).
4. Gates, C. A., 42, 4609f.
5. Kharasch, J. Am. Chem. Soc., 64, 333 (1942).
6. Nenitzescu, Isacescu, and Ionescu, Ann., 491, 210 (1931).
7. Patai and Bergmann, J. Am. Chem. Soc., 72, 1034 (1950).

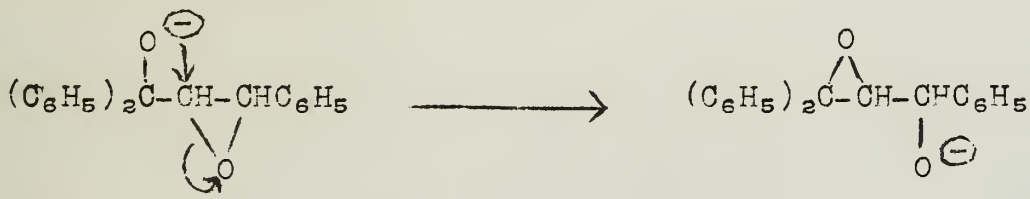
PARTICIPATION OF NEIGHBORING GROUPS IN ADDITION REACTIONS

Reported by Fabian T. Fang May 1, 1953

Neighboring groups which participate in nucleophilic replacement processes with relatively large driving forces[1] can also be expected to participate in addition reactions to the olefinic linkage initiated by electrophilic reagents[2]. The participation takes place either by a concerted mechanism or by a two-step process which involves a non-classical intermediate[3].

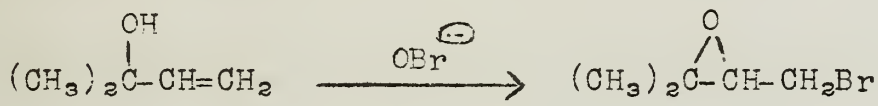


A classical analogue of the latter phenomenon can be found in the isomerization of 1,1,3-triphenyl-2,3-epoxy-1-propanol into 1,3,3-triphenyl-2,3-epoxy-1-propanol in the presence of cold, dilute methanolic potassium hydroxide[4].



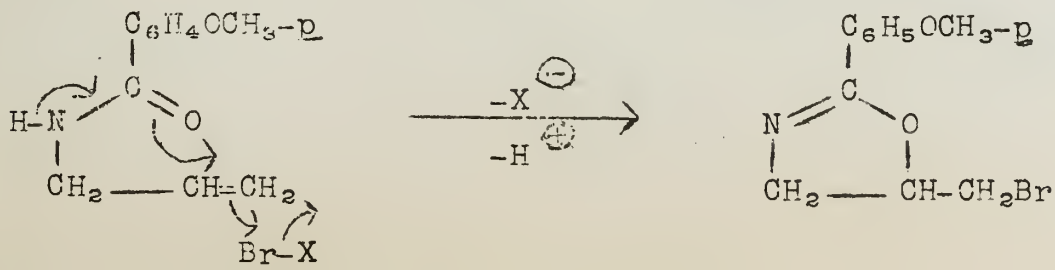
Neighboring Hydroxyl Group

Dimethylvinylcarbinol was found to give 1-bromo-2,3-epoxy-3-methylbutane on treatment with hypobromite, whereas allyl alcohol failed to yield the corresponding epoxy compound.[5].



Neighboring Acylamino Groups

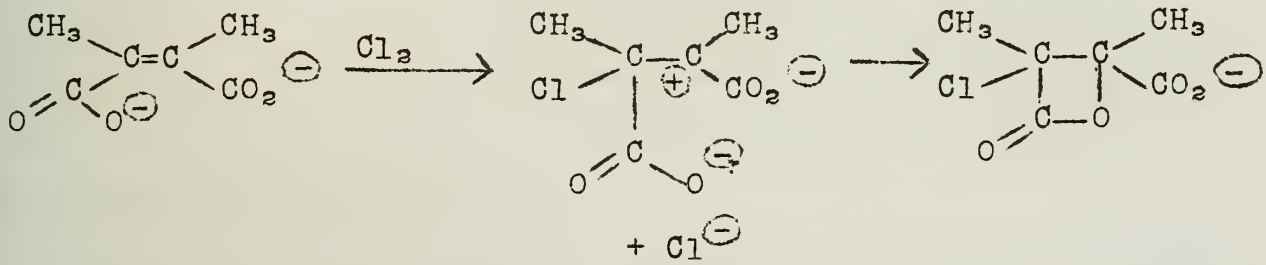
The acylamino groups are examples of so-called complex neighboring groups with rather large driving forces[2,6,7] and turn out to participate in addition reactions in a very useful manner. For example, N-p-methoxybenzoylallylamine gives the bromooxazoline in high yield when treated in acetic acid with N-bromosuccinimide[2].



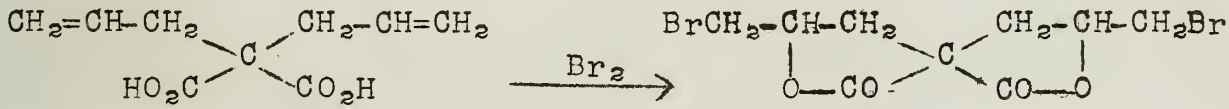
This type of reaction constitutes a way to set up three functional groups with a definite stereochemical relationship.

Neighboring Carboxyl Group

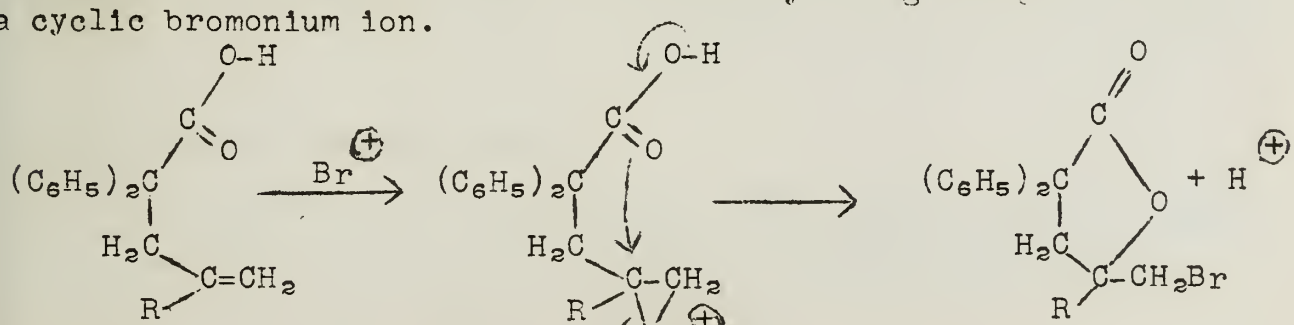
In an early study of the mechanism of addition reactions, Tarbell and Bartlett[8] reported the formation of halogenated β-lactones from the sodium salts of dimethylmaleic and dimethylfumaric acids by treatment with chlorine water or bromine water. The mechanism of a two-step addition process in fast succesion was proposed and the enhancement of ring closure by methyl substitution was noted.



It has long been recognized that γ,δ-unsaturated acids frequently react with electrophilic reagents to form δ-substituted-γ-pentanolactones instead of the simple addition product. Fittig and Hjelt[9] reported in 1883 the lactonization of diallylacetic, allylmalonic, and diallylmalonic acids by treatment with bromine or hydrobromic acid. The interesting formation of nonodilactones was observed in the last case.



Craig and Witt[10] found that lactonization occurred when 2,2-diphenyl-4-pentenoic and 2,2-diphenyl-4-methyl-4-pentenoic acids were treated with sulfuric acid or phosphoric acid to give the valerolactones in excellent yields. The same acids reacted with bromine to give good yields of the corresponding bromovalerolactones. The reaction scheme proposed by Craig[11] might involve a cyclic bromonium ion.



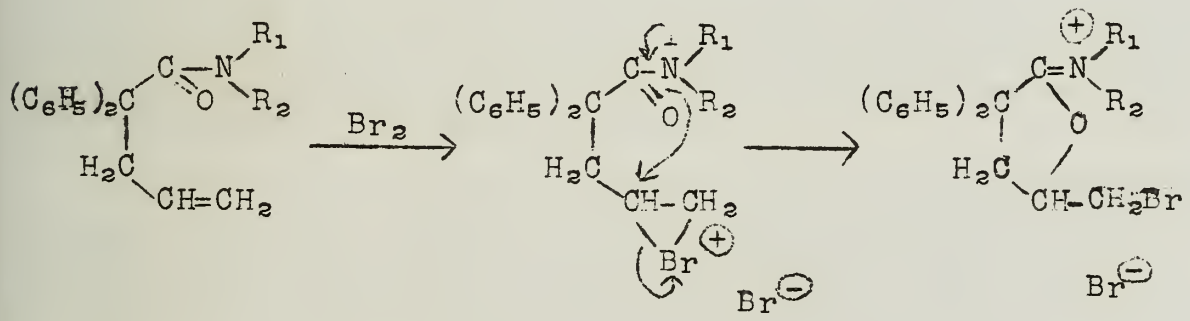
R = H or CH_3

The fact that 2,2-diphenyl-4-methyl-4-pentenoic acid lactonizes more readily with bromine or sulfuric acid than does 2,2-diphenyl-4-pentenoic acid suggests that the methyl group facilitates attack at the γ-carbon atom to form the 5-membered ring. Analogous substituent effect was found in the acid hydrolyses of ethyl methallylacetamidomalonate and of ethyl allylacetamidomalonate[12].

Similar participation of neighboring carboxyl groups in addition reactions has been observed with oleanolic acid[13] and 2-phthalimido-4-pentenoic acid[14]. Lactonizations have been demonstrated by the use of acids, bromine, acetyl hypobromite[15], and mercuric salts[16] as electrophilic reagents. Even iodine (both alone and catalyzed by mercuric chloride) and cyanogen iodide have been shown to possess sufficient cationoid reactivity to bring about lactonization of γ,δ-unsaturated acids, the product in each case being a δ-iodo-γ-pentanolactone[17]. 2,2-Diphenyl-4-pentenoic acid, 9-allyl-9-fluorenecarboxylic acid, and 4-pentenoic acid all give the expected iodolactone when treated with cyanogen iodide. This was claimed as the first observed spontaneous reaction of cyanogen iodide with carbon-carbon double bond[18].

Neighboring Carboxamido Groups

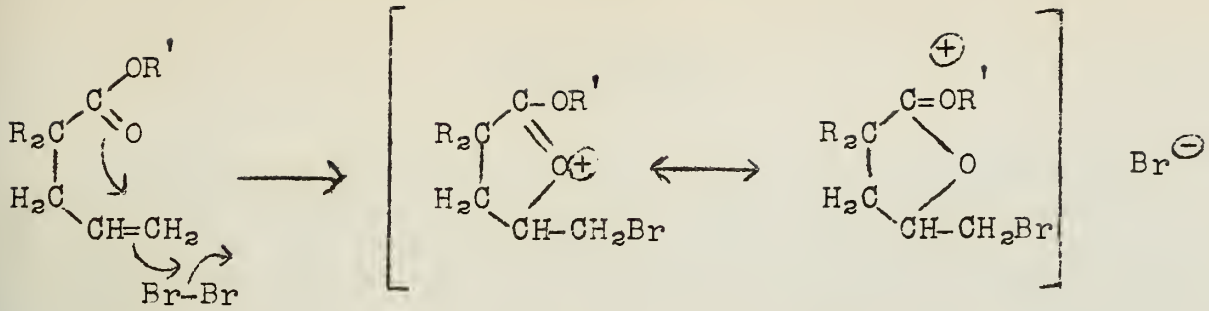
The participation of neighboring carboxamido groups in addition reactions has been investigated by Craig[11] with a number of amides derived from 2,2-diphenyl-4-pentenoic acid. When the amides are treated with bromine in carbon tetrachloride, a facile ring closure occurs in each case to give the corresponding 3,3-diphenyl-5-bromomethyl-2-iminotetrahydrofuran hydrobromide in good yield.



R_1 =	H	CH_3	C_2H_5	CH_2CH_2
R_2 =	H	CH_3	C_2H_5	CH_2CH_2

Neighboring Carbalkoxyl Groups

The esters of γ,δ-unsaturated acids also lactonize readily with the elimination of the alcoholic alkyl group[11,15,18]. The stereochemical proximity of the carbonyl oxygen atom to the γ-carbon atom allows it to participate in the formation of a resonance stabilized, cyclic oxonium salt.

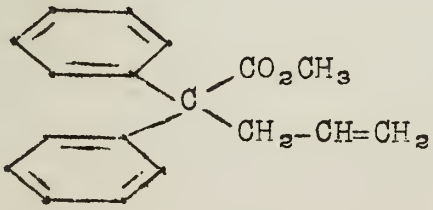


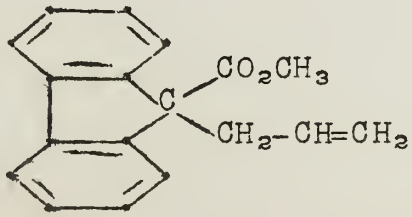
Among the possible reactions of the cyclic intermediate are: (1) the formation of the bromolactone and an alkyl bromide via an S_N2 type substitution with complete inversion; (2) the formation of the bromolactone and an alkyl bromide or an olefin via an S_N1 or E_1 mechanism, respectively; (3) the formation of the bromolactone and an olefin via an E_2 type elimination; and (4) the competing dibromide formation. The actual type of decomposition of the oxonium salt depends upon the nature of R and the nature of the reaction medium.

Ethyl bromide was isolated in considerable quantities from the bromination without solvent of diethyl allylbenzylmalonate; but hydrogen bromide was formed in 84% yield when the bromination was carried out in chloroform solution. The same ester reacted with acetyl hypobromite to give 50-65% of ethyl acetate and 63% of the bromolactone.

The d- and l-2-octyl esters of 2,2-diphenyl-4-pentenoic acid reacted separately with bromine in chloroform solution to give 39% of the 2-bromooctanes with 97.5% and 98.5% inversion of configuration, respectively. However, the neopentyl ester of the same acid gave on bromination 41% of the bromolactone and 59% of hydrogen bromide. The steric hindrance of the neopentyl group largely eliminates bimolecular attack and favors solvolytic reactions with rearrangement of the carbon skeleton.

Substitution in the α-position of γ, δ -unsaturated esters exerts remarkable influence on the relative extent to which dibromide formation competes with bromolactone formation[9,15]. Methyl 2,2-diphenyl-4-pentenoate was found to give virtually quantitative yields of the bromolactone[10,11], whereas the apparently similar methyl 9-allyl-9-fluorenecarboxylate gave 33% of the dibromide in addition to a 48% yield of the bromolactone[15]. It is obvious that the coplanar benzene rings of the fluorene derivative exhibit a smaller steric effect than that exhibited by the diphenyl compound.





BIBLIOGRAPHY

1. Winstein and Grunwald, J. Am. Chem. Soc., 70, 828 (1948).
2. Winstein, Goodman and Boschan, ibid., 72, 2311 (1950).
3. Winstein, Abstracts of Papers, Eleventh National Organic Chemistry Symposium of the American Chemical Society (June 1949), p. 72.
4. Kohler, Richtmyer and Hester, J. Am. Chem. Soc., 53, 205 (1931)
5. Winstein and Goodman, unpublished work.
6. Winstein, Hanson and Grunwald, J. Am. Chem. Soc., 70, 812 (1948).
7. Acker, Organic Seminar, University of Illinois, March 9, 1951.
8. Tarbell and Bartlett, J. Am. Chem. Soc., 59, 407 (1937).
9. Fittig and Hjelt, Ann., 216, 52 (1883).
10. Craig and Witt, J. Am. Chem. Soc., 72, 4925 (1950).
11. Craig, ibid., 74, 129 (1952).
12. Goering, Cristol and Dittmer, Abstracts of Papers, 113th Meeting of the American Chemical Society (April 1948), p. 69L.
13. Winterstein and Hämmerle, Z. physiol. Chem., 199, 56 (1931).
14. Gaudry and Godin, Abstracts of Papers, 123rd Meeting of the American Chemical Society (March 1953), p. 14M.
15. Arnold, Campos and Lindsay, J. Am. Chem. Soc., 75, 1044 (1953).
16. Rowland, Perry and Friedman, ibid., 73, 1040 (1951).
17. Arnold and Lindsay, ibid., 75, 1048 (1953).
18. Arnold and Lindsay, Abstracts of Papers, 122nd Meeting of the American Chemical Society (September 1952), p. 21M.

BASICITY OF AROMATIC HYDROCARBONS AND THE ISOMERIZATION OF THE METHYL BENZENES

Reported by Harry W. Johnson, Jr. May 1, 1953

The basicity of aromatic hydrocarbons has been the subject of several investigations in recent years. Frey[1] has reported the earlier work in the field.

Klatt[3] noted that aromatic hydrocarbons were soluble in liquid HF in the order benzene > toluene > m-xylene. Brown[2], who corrected Klatt's data for the vapor pressure of the hydrocarbon, obtained the opposite order. Hammett[4] has suggested that the results obtained by Klatt were explicable on the basis of the equatio

$$HF + Ar \rightleftharpoons ArH^{+} + F^{-}$$

McCaulay and Lien[5] studied the reactions of the methylated benzenes with $HF-BF_3$ and obtained values for the relative basicities of the compounds, and Brown[2,6] studied the relative basicities of the same series toward HCl (by determination of the Henry's law constant for the solubility of HCl in the hydrocarbon). Kilpatrick[7] has measured the relative basicities of the methylated benzenes toward HF through measurement of the conductance of a solution of the hydrocarbon in HF. The results of the studies mentioned are summarized in Table I.

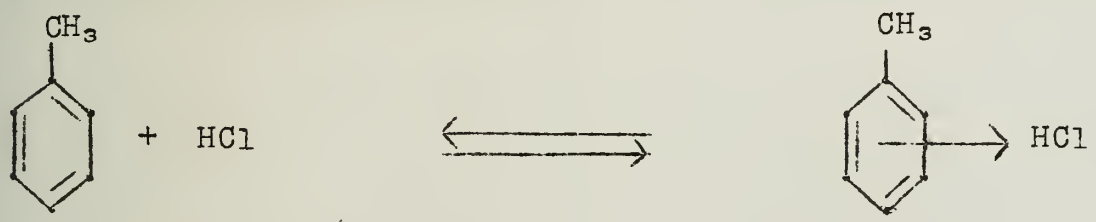
Table I
Relative Base Strengths of Hydrocarbons Toward Various Acids

Hydrocarbon	Relative Basicity HCl[2]	Relative Basicity $HF-BF_3$[2]	Relative Basicity HF[7]	Relative Activity (Halogenation)[2]
Benzene	0.61	--	0.09	0.0005
Toluene	0.92	0.01	0.63	0.157
p-Xylene	1.00	1.0	1.00	1.00
o-Xylene	1.1	2	1.1	2.1
m-Xylene	1.26	20	26	200
Pseudocumene (1,2,4)	1.36	40	63	340
Hemimellitine (1,2,3)	1.46	ca 40	69	400
Mesitylene (1,3,5)	1.59	2800	13000	80000
Durene (1,2,4,5)	--	120	--	1400
Prehnitine (1,2,3,4)	1.63	170	--	2000
Isodurene (1,2,3,5)	1.67	5600	16000	240000
Pentamethylbenzene	--	8700	29000	360000
Hexamethylbenzene	--	89000	97000	--
Ethylbenzene	1.06	--	--	0.13
i-Propylbenzene	1.24	--	--	0.080
t-Butylbenzene	1.36	--	--	0.050

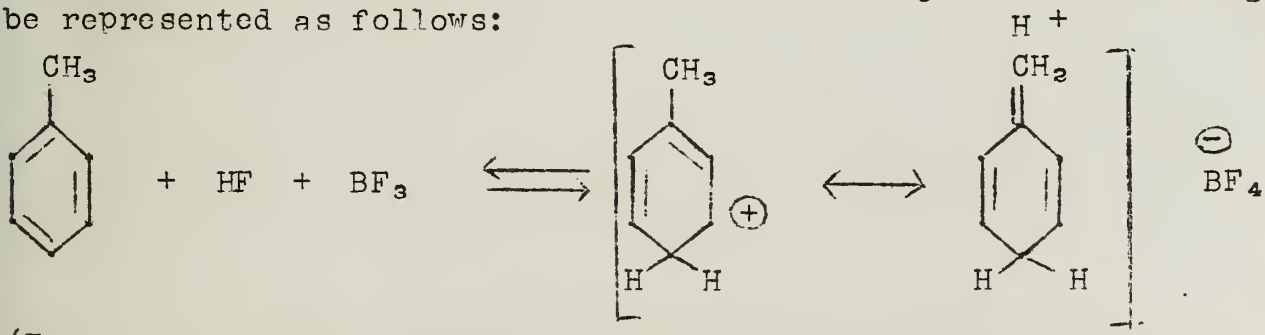
Brown[2] noted than inversions in the order of basicity occurred in the relative basicities of some members of the series toward HCl as compared with $HF-BF_3$ (for example, mesitylene is more basic than durene toward $HF-BF_3$, while the order is the reverse toward HCl; and m-xylene, mesitylene and isodurene are far more basic toward $HF-BF_3$ than their basicity toward HCl would indicate), and that in the cases where the inversions occurred the relative ease of halogenation followed the basicity toward $HF-BF_3$ rather than HCl.

Further, the complexes formed with the two reagents had different properties. The complexes formed with HCl were colorless, non-conducting solutions which did not exchange nuclear hydrogen for deuterium with DCl, while the complexes with $HF-BF_3$ are highly colored, conducting solutions which do exchange nuclear hydrogen for dueterium with DCl.[2,8,9] (Brown[9] and others[10] have discovered that although $AlCl_3$ and $AlBr_3$ do not react with the corresponding HX in the dry state or in saturated hydrocarbons, they do react in the presence of an aromatic hydrocarbon to give colored, highly conducting systems which are good solvents for the aluminum halides Thus, these systems would seem to be in the same class as the $HF-BF_3$-Ar complexes discussed above.)

Brown[2] accounts for the differences noted above with the assumption that two different types of interactions are involved. For the complex between HCl and the hydrocarbons he suggests that a π-complex is involved. The molecular orbital picture of benzene has the π-electron cloud in two rings above and below the nucleus, and it is suggested by Brown that the HCl interacts with the cloud without seriously deforming it and without the proton becoming attached to any particular carbon atom of the nucleus. This is the picture of Dewar[12] for a π-complex, and might be represented as follows:



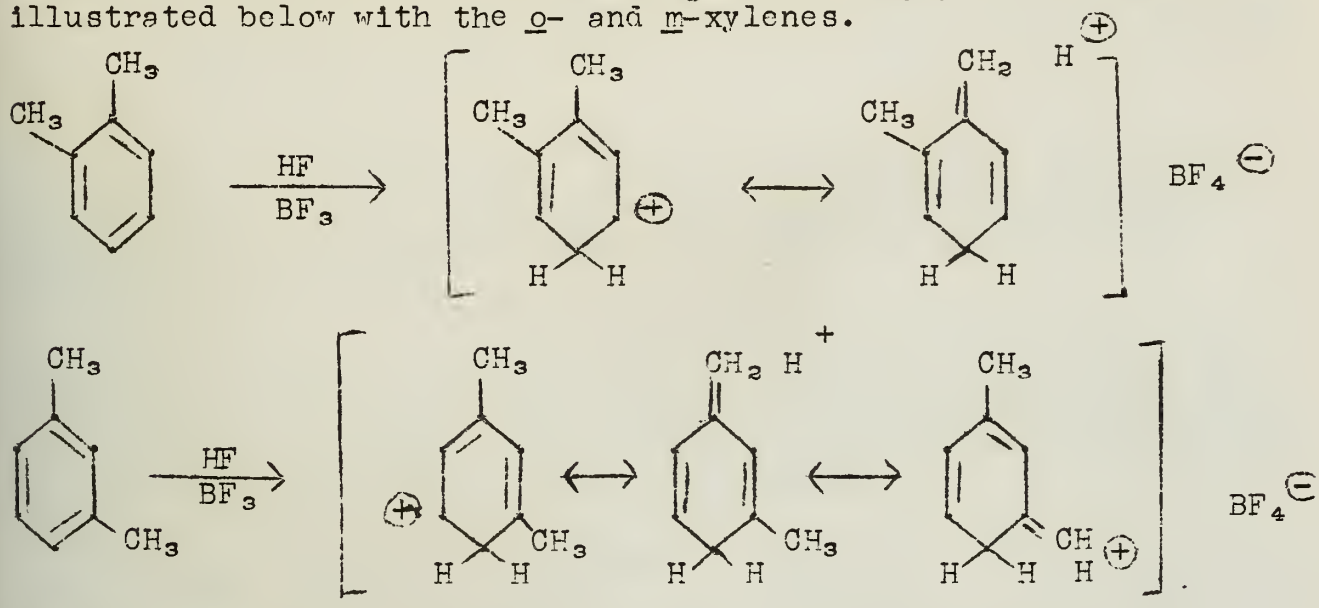
For the interaction of the aromatic compound with $HF-BF_3$, Brown[2] postulates the formation of a carbonium ion (or sigma complex) in which the proton is attached to a single carbon atom of the nucleus by a σ-bond (hence the name) which is stabilized by resonance. In this complex the π-electron cloud of the nucleus has been seriously distorted, compared with the π-complex, where little distortion is postulated. The complex of $HF-BF_3$ with toluene might be represented as follows:



(The ion in which the proton has been added to the carbon atom ortho to the methyl group is equally likely.)

The stability of the HCl complexes is relatively insensitive to the number or position of added methyl groups (note the range of basicities of the methylated benzenes toward HCl). The range of basicities of the methylated benzenes toward $HF-BF_3$ is much greater, and the relative basicity of isomers having more than one

methyl group in a position to stabilize the ion by hyperconjugation is much greater than those in which only one methyl group is in a position to stabilize the ion through hyperconjugation. This is illustrated below with the o- and m-xylenes.



In the case of the o-xylene, only one methyl group contributes through hyperconjugation, while in m-xylene both may contribute.

Evidence[2] seems to be accumulating which indicates that the full electron donating ability of the methyl group is not realized in systems in which no electron deficiency occurs. For example, the presence of a methyl group does not greatly affect the acidity of benzoic acids or the basicity of anilines, but does greatly influence the rate of solvolysis of phenylcarbinyl halides. In the systems at hand, the HCl complex has a π-electron cloud which is not seriously distorted, and, therefore, the influence of the methyl groups be smaller (operating predominantly through an inductive effect) than in the case of the HF-BF_3 complex in which the methyl group can stabilize the carbonium ion through hyperconjugation as illustrated above.

In postulating two types of complexes between electrophilic reagents and aromatic nuclei, Brown differs from Dewar[2], who would prefer to regard all such complexes as being of the π-variety. Since two types are apparently observed experimentally, and since the substitution reactions seem to parallel the σ-complex stability, Brown postulates that the stability of the σ-complex is the important factor in aromatic substitution rather than the stability of the π-complex as postulated by Dewar.

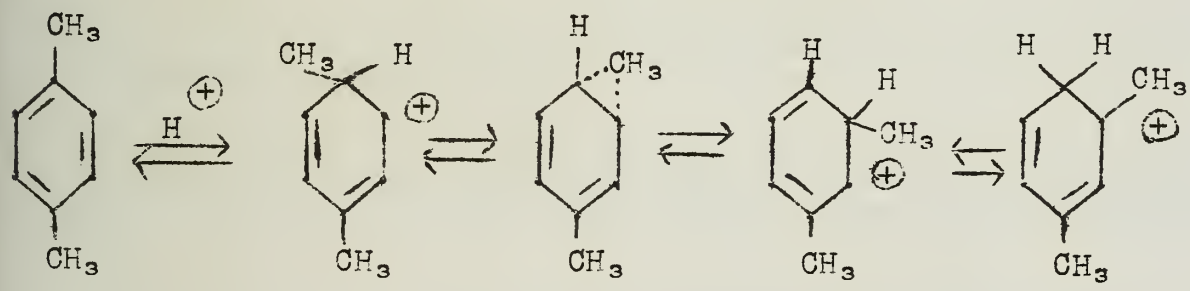
APPLICATION TO THE ISOMERIZATION OF THE METHYLBENZENES

McCaulay and Lien[12] have studied the isomerization of the xylenes and trimethylbenzenes with HF-BF_3 at various temperatures. They found that at 80 and 120° the xylenes rearrange to mixtures of xylenes, toluene and trimethylbenzenes, of which the xylene fraction has the equilibrium concentration of isomers (as calculated by Taylor) if the amount of BF_3 present was small (0.13 mole BF_3/mole hydrocarbon or less), but that with increasing amounts of BF_3

the amount of m-xylene increased until a value of 100% was reached with 3 moles BF_3/mole hydrocarbon. At 30° it was noted that no disproportionation occurred although isomerization was complete, which indicates that the energy of activation is less than the energy of activation of disproportionation. The kinetics of rearrangement of p-xylene were studied at 3 and 30°, and it was found that the reaction was first order in xylene with an activation energy of 12.7 kcal./mole.

In the isomerization of the trimethylbenzenes it was found that a plot of the mesitylene content of the product vs. the BF_3 concentration yielded a straight line, and in all cases in which the BF_3 content was greater than 1 mole/mole hydrocarbon only mesitylene was obtained.

In both cases it will be noted that when sufficient BF_3 was present to complex the product as the Ar-HF-BF_3 complex, the only isomer obtained was that corresponding to the strongest base toward the isomerizing mixture. The mechanism suggested for the rearrangement is shown below for the case of p-xylene.



(A) (AB) (B) (C)

m-Xylene is the strongest base (toward HF-BF_3) of the xylene isomers, and since its salt is the most stable, isomerization toward the m-isomer is favored.

On the basis of this work, it is possible that the formation of m-dialkylbenzenes or 1,3,5-trialkylbenzenes in the Friedel-Crafts reaction proceeds after the formation of the "normal" products, but the occurrence of such a sequence is not required.

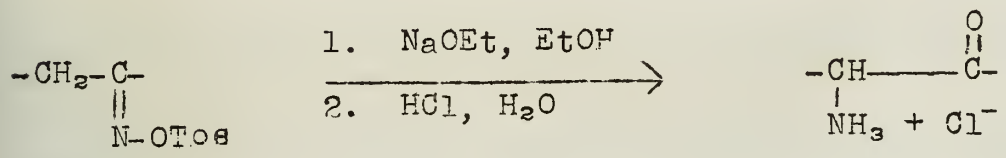
BIBLIOGRAPHY

1. S.E. Frey, Univ. of Ill. Seminar Abstracts, 38 (1951-1952).
2. H. C. Brown and J.D. Brady, J. Am. Chem. Soc., 74, 3570 (1952).
3. W. Klatt, Z.anorg.allgem.Chem., 234, 189 (1937).
4. L.P. Hammett, "Physical Organic Chemistry", McGraw-Hill Book Co, Inc., New York, N. Y., 1940, pp. 293-294.
5. D.A. McCaulay and A.P. Lien, J. Am. Chem. Soc., 73, 2013 (1951).
6. H.C. Brown and J.D. Brady, ibid., 71, 3573 (1949).
7. M. Kilpatrick and F.E. Luborsky, ibid., 75, 577 (1953).
8. A. Klit and A. Langseth, Z.physik.Chem., 176, 65 (1936).
9. H.C. Brown and H. W. Pearsall, J. Am. Chem. Soc., 74, 191 (1952).
10. D.D. Eley and P.J. King, J. Chem. Soc., 4972 (1952).
11. M.J.S. Dewar, "Electronic Theory of Organic Chemistry", Oxford University Press, New York, N. Y., 1949.
12. D.A. McCaulay and A. P. Lien, J. Am. Chem. Soc., 74, 6246 (1952).
13. C. K. Ingold, C. G. Raisin and C. L. Wilson, J. Chem. Soc., 1637 (1936).

THE NEBER REARRANGEMENT

Reported by Lewis I. Krimen May 1, 1953

Introduction. About 25 years ago Neber discovered that certain oximes in the presence of p-toluenesulfonic acid did not undergo a normal Beckmann rearrangement to give the amide but instead yielded alpha-aminoketones.[1] Neber and his coworkers conducted a series of investigations[1,2,3,4,5] in an attempt to

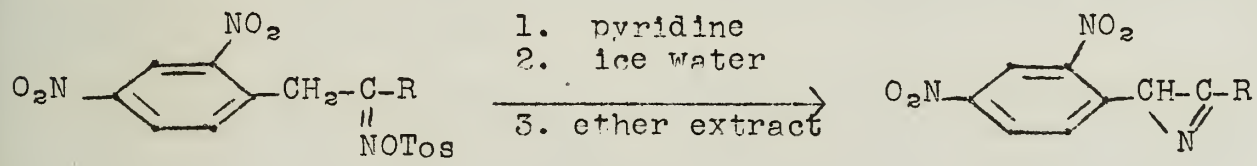


determine the course of the rearrangement and succeeded in two cases[3,4] in isolating unstable intermediates whose assigned structures (IA, IB) were considered to provide a satisfactory explanation for the entire reaction mechanism. The presumed substance, 2-(2,4 dinitrophenyl)-3-methyl-2-azirine (IA) was well characterized through analysis and molecular weight determinations.

Until recently this novel reaction has received very little attention and Neber's suggestion that the unstable intermediates contain an azacyclopropene ring (azirine ring system)[6] warrants critical examination.

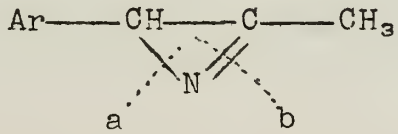
Cram and Hatch[7] undertook the present investigation in order to substantiate or disprove the original proposal of the azirine structure of the intermediates and to elaborate in more detail the mechanism and scope of the entire rearrangement.

Reactions of the Azirine Ring System. The reactions of Cram's investigation were conducted on compound IA, which was prepared from 2,4 dinitrophenylacetoneoxime-p-toluenesulfonate as follows:



IA, R = CH_3
IB, R = C_6H_5

The structural evidence is most simply explained on the basis of the azacyclopropene ring.



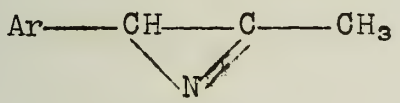
The ring has been opened at "a" by catalytic hydrogenation using Raney nickel to give a semi-dark solid which when chromatographed on alumina produced 2,4 dinintrophenylacetone. An imino compound was probably produced which hydrolyzed during the chromatographic

stage. Hydrogenation over a palladium-carbon catalyst in the presence of acetic anhydride produced two isomeric vinyl acetamide compounds. The susceptibility of the carbon-nitrogen single bond of the three member ring to hydrogenolysis is explained as a consequence of the strain associated with the azirine ring and with the stabilizing effect of the nitro groups upon the transition state of the reduction reaction.

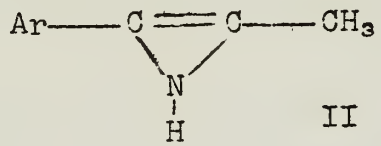
Treatment of the azirine with lithium aluminum hydride reduced the double bond at "b" to give an ethylenimine which was characterized through its tosyl derivative.

Attempts to produce optically active azirine (IA) both through resolution and by asymmetric synthesis failed.

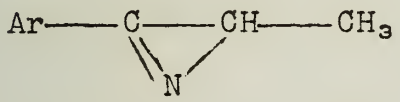
<u>The Structure of the Intermediate in the Neber Rearrangement</u>.[7] While Neber postulated structure I for the intermediate, several others have been proposed. These structures are:



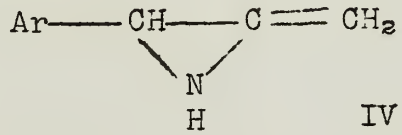
I



II



III

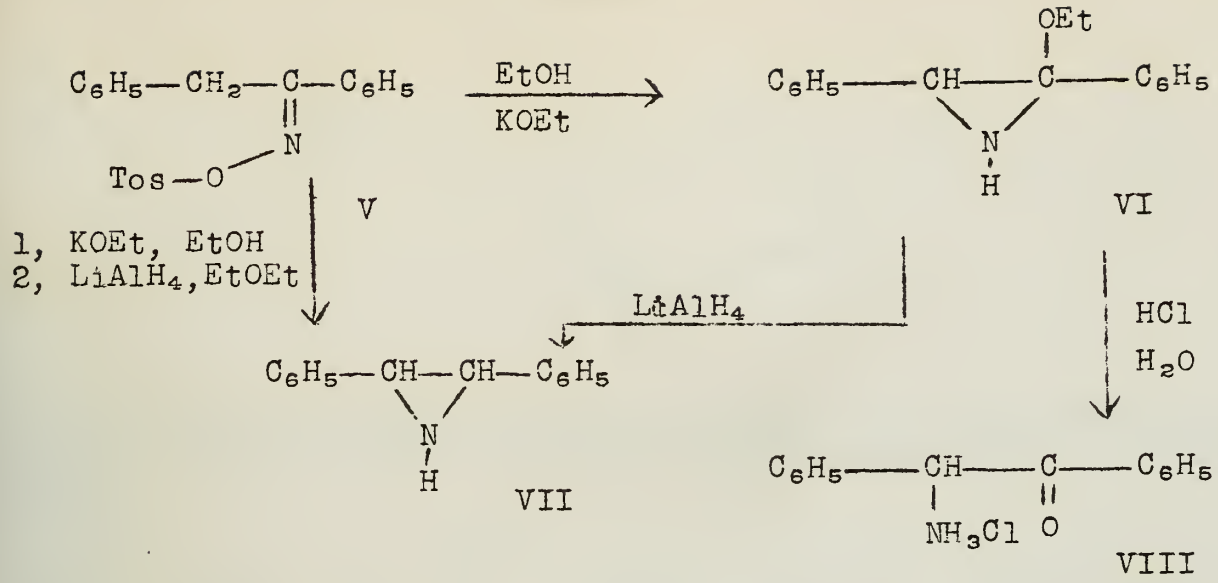


IV

Of these four tautomerically related structures III is inconsistent with both the hydrolytic behavior of the intermediate as noted by Neber, as well as with the reduction reactions reported by Cram. Structures II and IV contain an N-H linkage and since this band[8] is missing in the infrared spectrum of the intermediate, these two structures become unlikely.

In contrast, structure I is consistent with both the chemical and spectral data. The infrared spectrum of the intermediate has a band occurring at 5.55μ which is absent in that of the derived ethylenimine and can be attributed to the $>$C=N- stretching vibration present in the intermediate and absent in the imine.

<u>The Neber Rearrangement in the Desoxybenzoin System</u>.[9] Although Neber converted the <u>p</u>-toluenesulfonate of desoxybenzoinoxime (V) to desylamine hydrochloride (VIII) no[4] intermediates were isolated. Cram and Hatch repeated this investigation with slight modifications to give <u>cis</u>-2,3-diphenylethylenimine (VII)



Compound VI was demonstrated to be 2,3-diphenyl-2-ethoxyethylenimine and apparently represents the first known example of its structural class.[10]

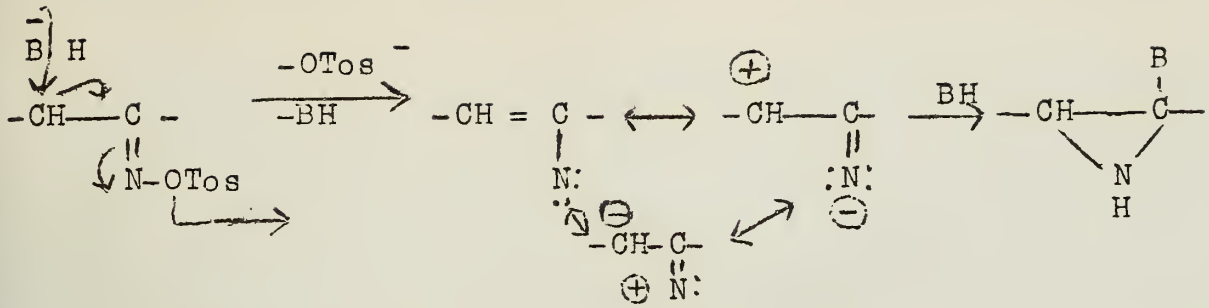
Evidence for the assigned structure is as follows:

(1) The molecule possesses a molecular formula of $C_{16}H_{17}NO$. (2) The substance contains one ethoxyl group. (3) When hydrolyzed by aqueous acid, the compound gave desylamine hydrochloride. (4) When reduced with lithium aluminum hydride, the compound gave cis-2,3-diphenylethylenimine (VII). (5) The ultraviolet absorption spectrum closely resembles that of cis-2,3-diphenylethylenimine. (6) The band in the infrared spectrum that occurs at 2.9μ is evidence for an N-H bond in the molecule. The same band appears in the spectrum of cis-2,3-diphenylethylenimime (VII) and is undoubtedly due to an N-H stretching frequency.

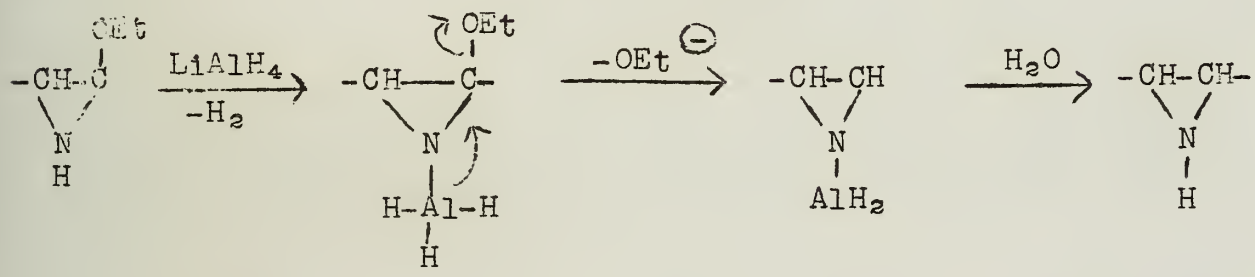
In order to obtain further evidence regarding the intermediates in the Neber rearrangement, the p-toluenesulfonate of p,p'-dichlorodesoxybenzoinoxime was prepared and submitted to the usual reaction conditions. Although no ethoxyethylenimine was isolated good evidence for its existence was obtained.

Structural Features Necessary for the Neber Rearrangement.[9] Since all the systems that have been submitted to the Neber rearrangement contain a methyl or methylene group alpha to a ketone function, the question arises as to whether the reaction is limited to compounds of such structural types. An E_2 reaction to form nitriles resulted when oxime tosylates of aldehydes were submitted to reaction conditions of the Neber rearrangement, and, therefore, any extension of the rearrangement could involve only alpha-methinylketoxime tosylates.

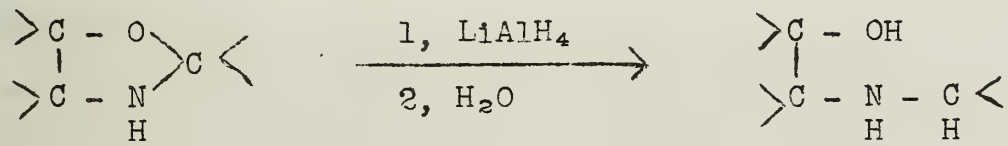
The Mechanism of the Neber Rearrangement.[9] The first step in the over-all reaction can be generalized in terms of a base induced 1,3 elimination reaction (with ring closure) upon which has been superimposed a 1,2 addition reaction. This picture is essentially the same as the one suggested by Neber.[4]



A formulation which satisfies all the facts known about the lithium aluminum hydride reduction of the intermediate is pictured below.



The reduction of the ethoxyethylenimines with lithium aluminum hydride possibly goes as shown in the formulation.



The preferential cleavage of the O-C bond is analogous to the well-known reduction of amides to amines, and the recently reported reduction of oxazolidines to N-substituted alpha-amino alcohols.[11]

BIBLIOGRAPHY

1. P. W. Neber and A. Friedolsheim, Ann., 449, 109 (1926).
2. P. W. Neber, A. Burgard, and W. Thier, ibid., 526, 277 (1936).
3. P. W. Neber and A. Burgard, ibid., 493, 281 (1932).
4. P. W. Neber and G. Huh, ibid., 515, 283 (1935).
5. P. W. Neber and A. Uber, ibid., 467, 52 (1928).
6. A. M. Patterson and L. T. Capell, "Ring Index", Reinhold Publishing Corp., New York, N. Y., 1940, p. 3.
7. D. Cram and M. Hatch, J. Am. Chem. Soc., 75, 33 (1953).
8. H. M. Randall, R. Fowler, N. Fuson, and J. R. Dangl, "Infrared Determination of Organic Structures", D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 6.
9. M. Hatch and D. Cram, J. Am. Chem. Soc., 75, 38 (1953).
10. J. Fruton in Elderfield's, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 61, and F. King, J. Chem. Soc., 1318 (1949).
11. E. Bergmann, D. Lavie, and S. Pinchas, J. Am. Chem. Soc., 73, 5662 (1951).

PHOTOCHEMICAL REACTIONS[8,14]

Reported by Ruth J. Adams May 8, 1953

Although in solution photochemical reactions usually proceed by paths involving free radicals and radical-ions, it is in some instances possible to use light in promoting, under mild conditions chemical reactions which are known to have ionic mechanisms. For example, esterification of trans-hexahydroterephthalic acid[15] has been found to proceed in the absence of strong acids or bases to give a fifty percent yield of the trans-dimethyl ester simply by the irradiation for two weeks of a methanolic solution of the acid

PHOTO-ISOMERIZATION

In perhaps no other class of reactions is light a more useful synthetic tool than it is in the isomerization of organic compounds. Its utility in the interconversion of cis- and trans-forms is well known. In many cases, photoisomerization is the most convenient way to accomplish such conversions, in others, it is the only way, e.g., the preparation of cis-azobenzene from the normally obtained trans-azobenzene. Supposedly, because π bonds are weaker than σ bonds, the change from cis to trans and conversely proceeds by means of a diradical intermediate which is capable of free rotation around the central bond.

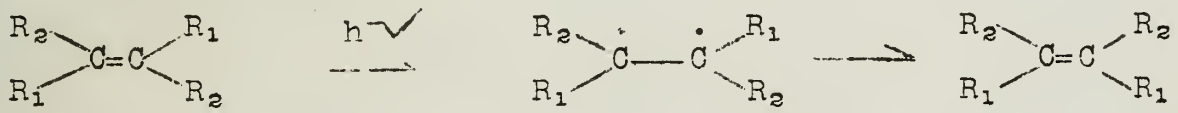
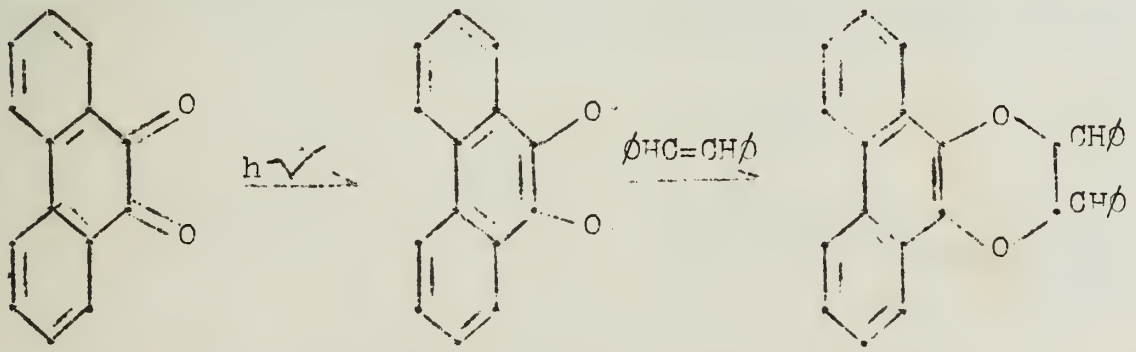


PHOTO-ADDITION

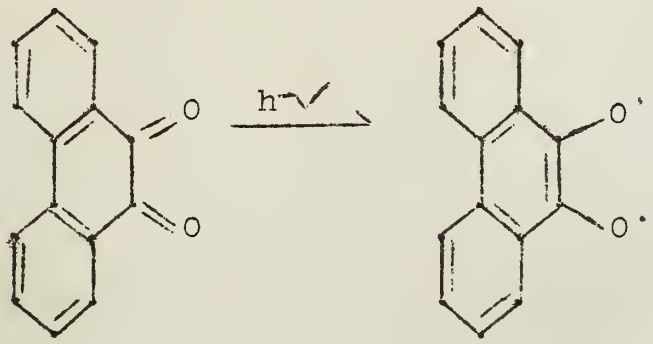
The light catalyzed production of free radicals or atoms and their subsequent addition to unsaturated compounds is exemplified by the photo-addition of the halogens, halogen acids, alcohols, mercaptans, thioacids, etc. to olefins. The monomeric addition of phenanthraquinones and phenanthraquinonimines to unsaturated compounds[11,13] is of some theoretical interest since it presumably occurs as the result of the formation of a diradical.



Similarly, the addition of benzaldehyde[9] to phenanthraquinones probably involves the initial production of the same type of radical. Acetaldehyde, p-anisaldehyde, and benzaldehyde add very rapidly, but the reaction is considerably slower with 2-methoxy-1-naphthaldehyde, possibly because of steric hindrance (ortho effect).[12]

Air is excluded in these reactions to prevent side reactions due to oxidation.

a)



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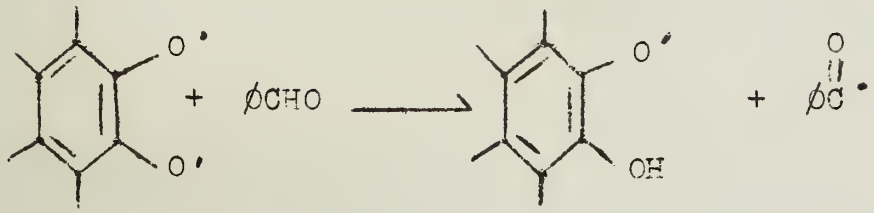

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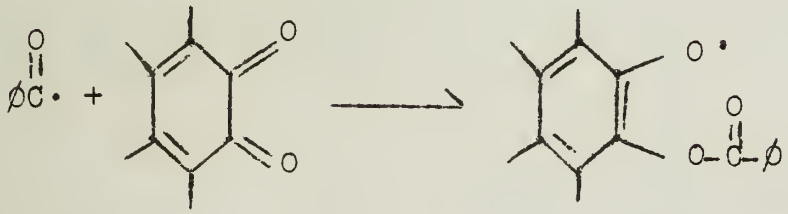

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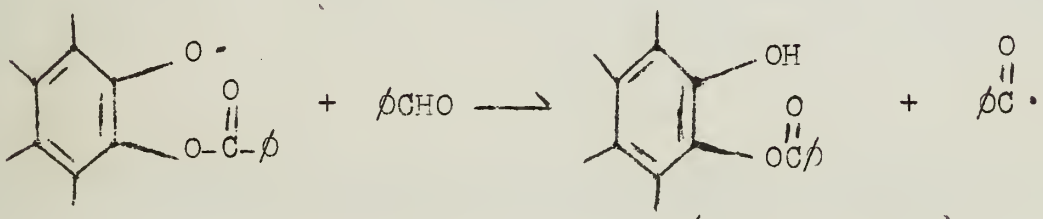
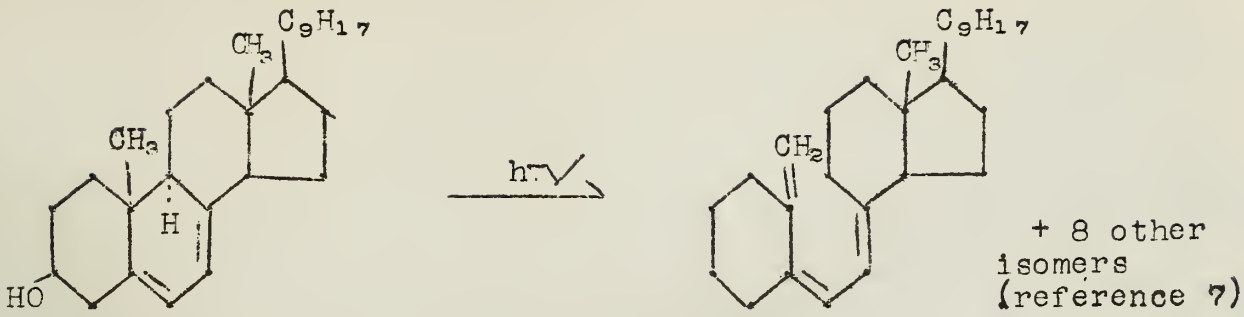


(quantitative)

PHOTO-REARRANGEMENTS

Photochemical intramolecular rearrangements provide the best synthetic route to some molecular species. Two such examples are given below.

(quantitative)
(reference 4)



Ergosterol Vitamin D_2

In a number of cases, glycidic ketones have been observed to isomerize under the influence of light to β-diketones.[3]

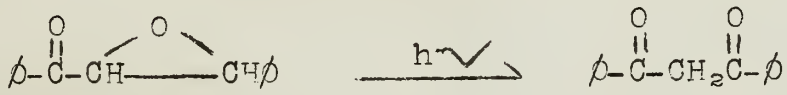
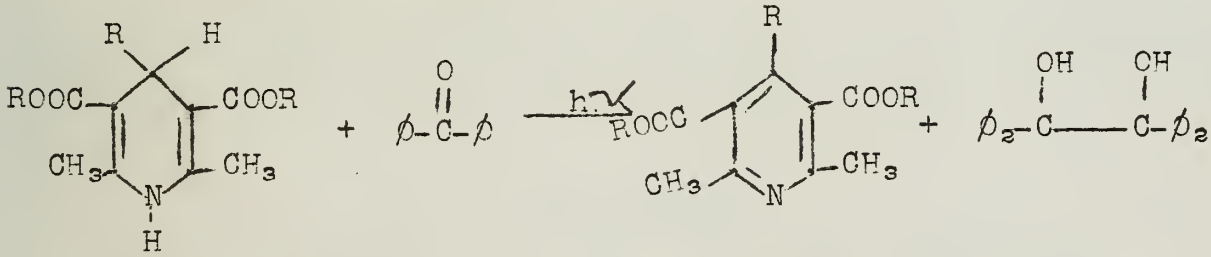
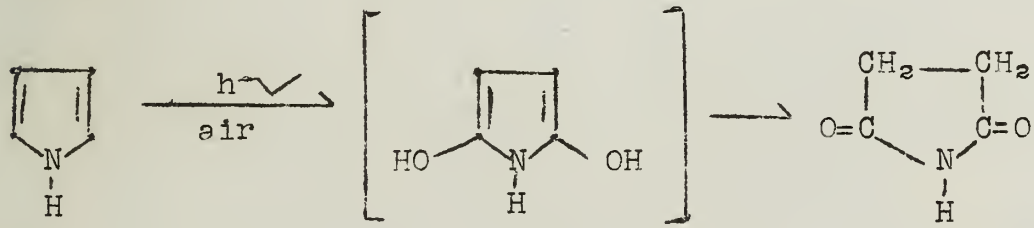


PHOTO-REDUCTION and-OXIDATION

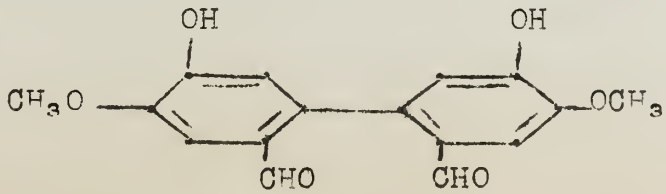
The classic example of photo-reduction is the formation of benzopinacol from benzophenone in the presense of isopropanol in nearly theoretical yield. Other readily oxidizable compounds may take the role of isopropyl alcohol, e.g.[5]



Pyrrole is changed completely by the action of sunlight into a variety of products, among which succinimide is formed in low yield.[4]



Anthraquinone[2] in xylene solution can be quantitatively oxidized to diphenic acid. Although 3-methoxy-4-hydroxybenzaldehyde remains unchanged when irradiated with red light, blue light is instrumental in causing a curious dehydrogenation. The product is 2,2'-diformyl-4,4'-dimethoxy-5,5'-dihydroxydiphenyl.[8]



CONCERTED PHOTOCHEMICAL REACTIONS

In recent times, there has been some relatively intensive study of photolysis reactions in the gaseous phase using known wavelengths and intensities of light at specified temperatures and pressures. Using mass-spectrographic and chemical methods, quantitative isolation and identification of virtually all the products arising from some photolysis reactions have been accomplished. Careful analysis of the data has shown that some products are the result of intramolecular concerted decompositions which involve no free radical intermediates. An example of this is found in the photochemistry of propionaldehyde.[1] At 3130 Å, nearly all the molecules that decompose, dissociate into ethyl and formyl radicals; however, the absorption of more energetic quanta at shorter wavelengths favors an intramolecular dissociation which yields ethane and carbon monoxide directly.

$$1)\quad CH_3CH_2CHO \longrightarrow CH_3CH_2\cdot + \cdot CHO$$

$$2)\quad CH_3CH_2CHO \longrightarrow CH_3CH_3 + CO$$

Addition of iodine to the reaction mixture results in the interception of the radicals formed in reaction (1) to give ethyl iodide as the product rather than ethane. Reaction (2) is unaffected by iodine.

Even though this field is just beginning to be explored with quantitative methods, it holds important implications for synthetic organic chemistry. By varying the wavelength, it may be possible to change the products of a photochemical reaction.

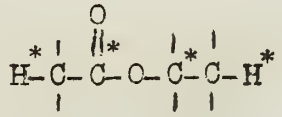
BIBLIOGRAPHY

1. Blacet and Pitts, J. Am. Chem. Soc., 74, 3382 (1952).
2. Benrath and Meyer, Ber., 45, 2707 (1912).
3. Bedforss, Ber., 51, 214 (1918).
4. Ciamician and Silber, Compt. Rend., [5], 10, I, 228.
5. Ciamician and Silber, Ber., 44, 1558 (1911).
6. Ciamician and Silber, Ber., 45, 1842 (1912).
7. Fieser and Fieser, "Natural Products Related to Phenanthrene", p. 168, Reinhold Publishing Co., New York, N. Y., 1949.
8. Houben, "Die Methoden der Organischen Chemie", Vol. II, p. 1221-1326, G. Thieme, Leipzig, Germany, 1925.
9. Moore and Waters, J. Chem. Soc., 1953, 238.
10. Organic Syntheses, Collective Vol. II, p. 71, John Wiley and Sons, Inc., New York, N. Y., 1943.
11. Schönberg and Awad, J. Chem. Soc., 1945, 197.
12. Schönberg, Awad, Latif and Moubasher, J. Chem. Soc., 1950, 374.
13. Schönberg and Moubasher, J. Chem. Soc., 1939, 1430.
14. Steacie, "Atomic and Free Radical Reactions", Reinhold Publishing Corp., New York, N. Y., 1946.
15. Stoermer and Ladewig, Ber., 47, 1803 (1914).

CONDENSATIONS INVOLVING ESTERS

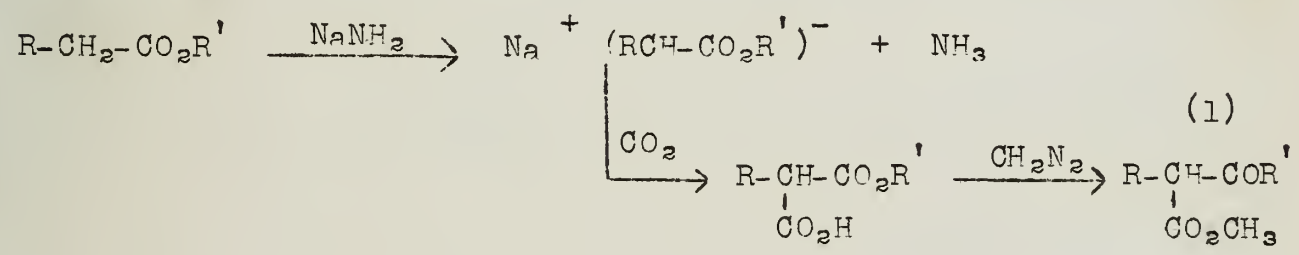
Reported by Leroy Whitaker May 8, 1953

There are four possible positions of reaction when a base attacks a carboxylic ester.[1] The carbonyl carbon and the α-hydrogen in the acyl portion of the ester generally enter into reaction with bases, but the α-carbon and the β-hydrogen in the alkoxy portion are also capable of reacting. These four possible positions of attack are marked by asterisks in the following general formula.



Reactions of the type involving attack at the α-carbon of the alkoxy portion are illustrated by the reaction of methyl benzoate and sodium methoxide to form dimethyl ether.[2] Reaction of the β-hydrogen is exhibited by the reaction of β-phenyl-ethyl mesitoate with potassim amide to yield mesitoic acid and styrene.[1] The other two possible positions of attack will be discussed in more detail.

In the presence of sodium amide there are two types of reactions exhibited by carboxylic esters.[3] One type involves reaction at the carbonyl carbon to form the corresponding amide, whi while the other consists in the removal of the α-hydrogen to form the ester anion. This latter type reaction is involved in the formation of half malonic acid esters (equation 1).



(1)

Either isopropyl magnesium bromide or sodium amide in ether will bring about the self-condensation of t-butyl acetate to give 40-50% yields of t-butyl acetoacetate.[4] Mixed condensations of esters with esters to form β-keto esters have also been observed.[5] These condensations have generally been done using sodium ethoxide or sodium or potassim triphenylmethide, but Hauser, et al., have used sodium amide for this type condensation.[5] These condensations proceed through the ester anion.

Esters will also react with active methylene compounds in the presence of a base. Phenoxyacetylacetophenone can be prepared by the action of ethyl phenoxyacetate on acetophenone in the presence of sodium ethoxide.[6] o-Xylylene cyanide reacts with ethyl oxalate in the presence of sodium ethoxide to give a quantitative yield of 1,4-dicyano-2,3-dihydroxynaphthalene.[7] Early work on the condensation of esters with ketones showed that in the presence of sodium ethoxide the products obtained were β-diketones.[6] In all the

above reactions the sodio derivative of the active methylene compound is first formed, and this reacts with the carbonyl carbon of the ester. The reaction is illustrated by equation 2.

$$CH_3COR + NaNH_2 \longrightarrow Na^+(CH_2COR)^- \xrightarrow{R'COOR''} R'COCH_2COR + NaOR'' \quad (2)$$

The influence of the structure of the ester on the two courses of reaction may be summarized by the following generalizations.[3] (a) Substitution of an α-hydrogen of an ester by a phenyl group favors the formation of the ester anion, whereas the substitution of an α-hydrogen by an alkyl groups favors the formation of the amide, the effect being especially marked by the introduction of a second alkyl group. (b) Substitution of alkyl groups in the alkoxy portion of an ester favors the formation of the ester anion, especially if the alkoxy portion becomes t-butoxy.

Hamell and Levine[8] found that the size and basic strength of the base used have a great effect upon the position of attack. They used three different lithium bases with ethyl isobutyrate and found that the weaker and less complex the base, the more likely it is that the attack will come at the carbonyl carbon.

In 1951 Hauser and Puterbaugh[9] simulated the Reformatsky type of reaction using t-butylacetate instead of an α-halo ester. The acetate was first converted to its sodio derivative by the use of sodium amide; zinc chloride was added at -70°, and then acetophenone was added. A 31% yield of t-butyl β-hydroxy-β-phenylbutyrate was obtained. The reaction is shown by equation 3.

$$CH_3COOC(CH_3)_3 \xrightarrow[2.\ ZnCl_2]{1.\ NaNH_2} ClZnCH_2COOC(CH_3)_3 \xrightarrow{C_6H_5-CO-CH_3} C_6H_5-\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}-CH_2COOC(CH_3)_3 \quad (3)$$

They then discovered that the same reaction could be brought about by using lithium amide without zinc chloride. The yields were higher by this method. The use of sodium amide alone failed.

On further investigation of the use of lithium amide to prepare β-hydroxy esters, Hauser and Puterbaugh[10] found that in order to minimize self-condensation of the ester and to ensure preferential metalation of the α-hydrogen, the t-butyl ester should be used. These possible side reactions and the main reaction in this method of preparation of β-hydroxy esters are illustrated by the following equations.

$$CH_3COOC(CH_3)_3 + LiNH_2 \rightarrow CH_3CONH_2 \quad / \quad LiCH_2COOC(CH_3)_3 \qquad (4)$$

$$LiCH_2COOC(CH_3)_3 \xrightarrow{CH_3COOC(CH_3)_3} CH_3COCH_2COOC(CH_3)_3$$

$$LiCH_2COOC(CH_3)_3 \xrightarrow{C_6H_5COCH_3} C_6H_5\underset{\underset{OLi}{|}}{C}(CH_3)CH_2COOC(CH_3)_3 \qquad (5)$$

$$C_6H_5\underset{\underset{OLi}{|}}{C}(CH_3)CH_2COOC(CH_3)_3 \xrightarrow{HOH} C_6H_5\underset{\underset{OH}{|}}{C}(CH_3)CH_2COOC(CH_3)_3 \qquad (6)$$

In general the yields of the β-hydroxy esters obtained by this method are comparable to those obtained in the Reformatsky reaction, and this method seems to be more convenient. One serious disadvantage of this reaction is that it is entirely satisfactory only with t-butyl esters.

REFERENCES

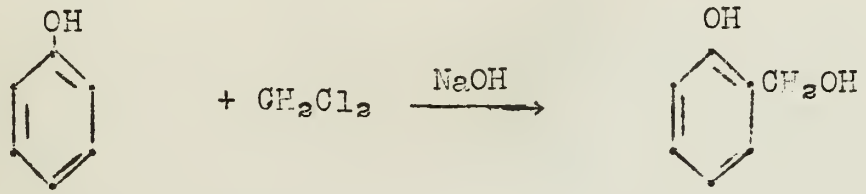
1. C. R. Hauser, J. C. Shivers, and P. S. Shell, J. Am. Chem. Soc., 67, 409 (1945).
2. A. Magnani and S. M. McElvain, ibid., 60, 813 (1938).
3. C. R. Hauser, R. Levine, and R. F. Kibler, ibid., 68, 26 (1946).
4. J. C. Shivers, B. E. Hudson, Jr., and C. R. Hauser, ibid., 65, 2051 (1943).
5. J. C. Shivers, M. L. Dillon, and C. R. Hauser, ibid., 69, 119 (1947).
6. R. von Walther, J. Prakt. Chem., 83, 171-82 (1911).
7. W. Wislicenus and W. Silberstein, Ber., 43, 1837 (1910).
8. M. Hamell and R. Levine, J. Org. Chem., 15, 162 (1950).
9. C. R. Hauser and W. H. Pauterbaugh, J. Am. Chem. Soc., 73, 2972 (1951).
10. C. R. Hauser and W. H. Puterbaugh, ibid., 75, 1068 (1953).

THE LEDERER-MANASSE REACTION

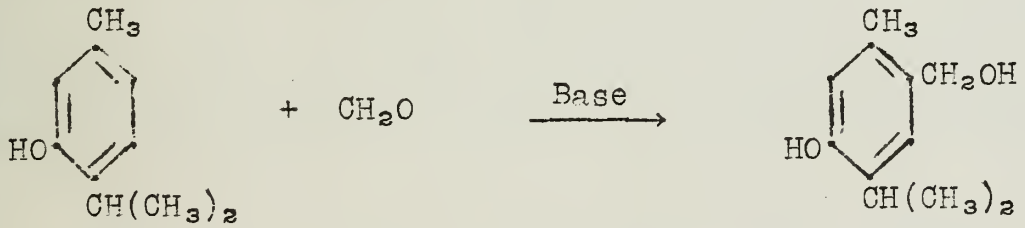
Reported by P. Wiegert May 8, 1953

Methylolphenols were first generally prepared by reduction of the corresponding aldehydes, acids, and amides with sodium amalgam However, the yields and availability of the starting materials mad a direct synthesis of the alcohols desirable.

The course to be followed in such a synthesis was first indic ed by Green[1] in 1880 when he announced the preparation of o-hydroxybenzyl alcohol by the condensation of phenol and methylene chloride in the presence of sodium hydroxide.



Various workers immediately tried to replace the methylene chloride with formaldehyde, but since acidic media were employed only resins and diphenylmethane derivatives were obtained. Baeyer[2] had already noticed this in 1872 when he reported that phenols react with aldehydes in the presence of acid, although the products were not identified. Lederer[3] and Manasse[4], working independently, then tried alkaline systems and accomplished the condensation of various phenols with formaldehyde. Under alkaline conditions the condensation of the alcohols is slower than is their rate of formation.



Lederer used weakly alkaline systems and effected completion of reaction by heating. Resin formation was minimized by keeping the heating period as short as possible. Manasse, on the other hand, preferred strong alkali and permitted the reaction to proceed at room temperature until the odor of phenol had disappeared. Several days were usually required. In spite of this difference in technique the claims of the two workers very largely coincided as to results, and their methods were combined in a single patent. However, the procedure of Manasse has come to be more or less standard.

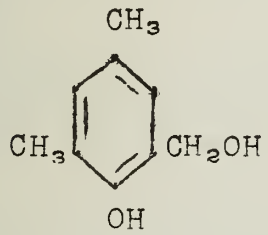
The original papers were almost devoid of experimental detail; indeed, the patent literature was about the only source of such information. Detailed experimental methods were then devised by Auwers[5] and associates. These workers also established definitely the identity of the products, most of these experiments being carried out with xylenols. Finally, in 1907 Auwers published a general review of the subject.[6] The original statements of Lederer

and Manasse, that the condensation occurs exclusively at the positions ortho and para to the hydroxyl group, were confirmed. Many bases effect the condensation, such as sodium and potassium hydroxide, calcium carbonate, zinc oxide, lead oxide, and sodium acetate.

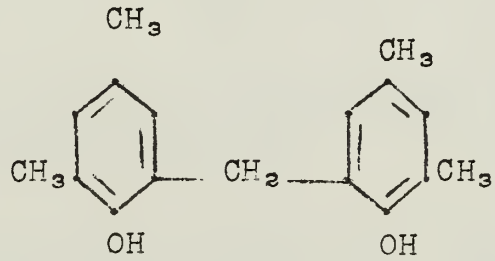
Strong alkali was found to favor formation of the para isomer in many instances. p-Xylenol, sodium hydroxide and formaldehyde gave an almost quanitative yield of the corresponding alcohol:

However, the above statement about the preponderance of the para isomer may have been influenced by the fact that its solubility is less than that of the ortho isomer and is thus easier to isolate pure.

Formation of diphenylmethane derivatives accompanies many of these reaction, but because of their lower solubility in most solvents they are quite easy to remove. Formation of this product is favored by increasing the strength of the base. For example, as. m-xylenol when condensed with formaldehyde in the presence of calcium carbonate gives the alcohol (I) in good yield but if sodium hydroxide is used (no matter how dilute) the main product is the diphenylmethane derivative, 3,3',5,5'-tetramethyl-2,2'-dihydroxy-diphenylmethane (II).

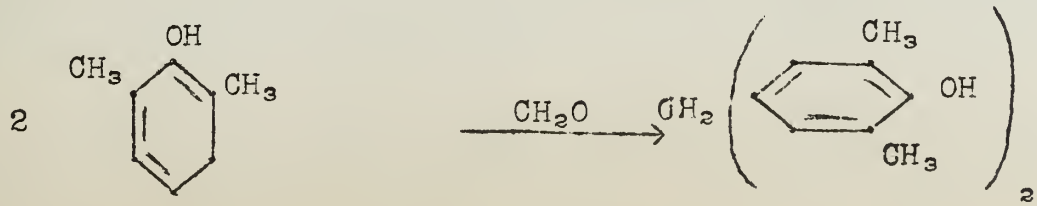


I

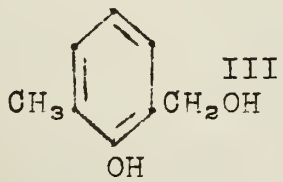


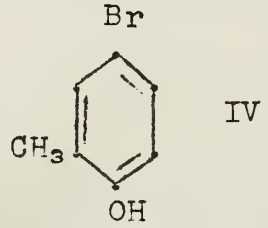
II

Base strength is not the only governing factor, however, for some phenols, e.g., β-naphthol or vic. m-xylenol give only the diphenylmethane derivatives no matter what base is used.

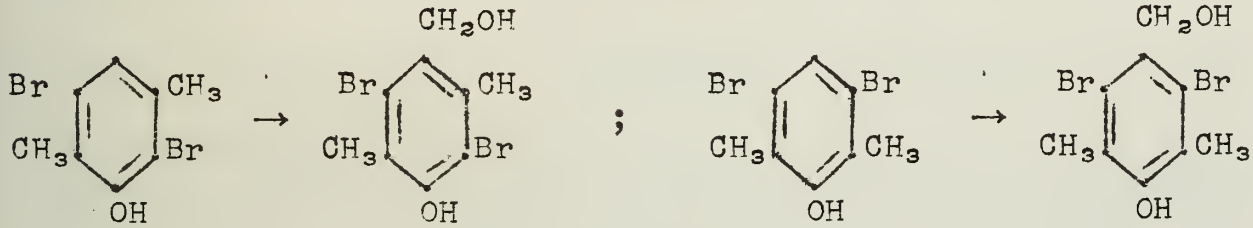


The presence of halogens or nitro groups may cause the reactio to fail completely. For example, it had been hoped to prepare o-homosaligenin (III) by reduction of the alcohol obtained by condensing formaldehyde with 2-methyl-4-bromophenol (IV).

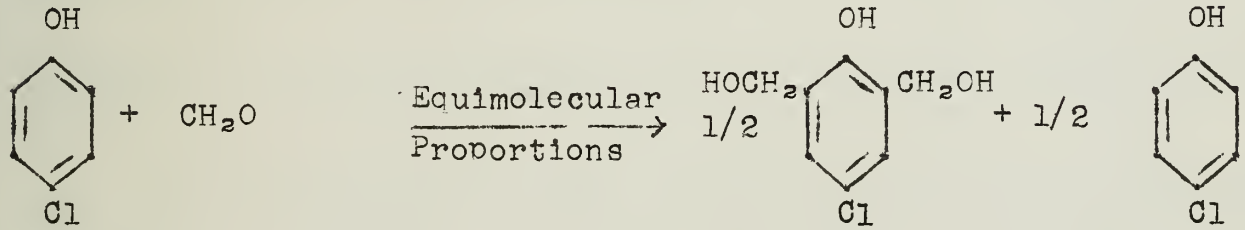




The first step of the process failed completely, however. Examples are known nontheless, in which bromine-containing phenols react almost quantitatively.



Sometimes the methylolphenol produced undergoes condensation more easily than does the original phenol.[12]

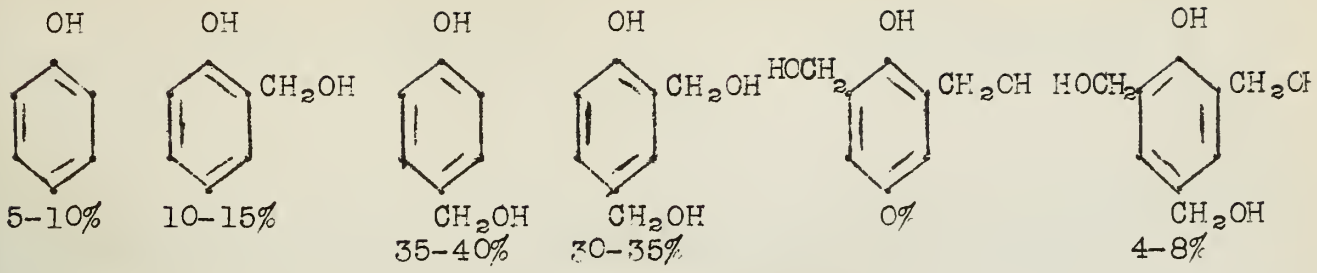


Most of the methylolphenols melt in the range 75-115° and on treatment with ferric chloride solution give the characteristic test. The tendency is toward a blue coloration.

Early workers had noted the formation of polyalcohols by repeated condensations, but in 1932 Granger[7] showed that such behavior was by no means as unusual as had been supposed. He demonstrated polyalcohol formation with phenol and o-cresol and indeed, showed that such behavior was to be expected with any phenol which has more than one ortho or para position open. Thus, for phenol the number of possible isomers is five (two mono-, two di-, and one tri-functional alcohol). Using the method sketched by Manasse, Granger found that when phenol was treated with an equimolecular quantity of formaldehyde, all the aldehyde underwent condensation with but two-thirds of the phenol. He was unable to isolate the higher derivatives, however.

An attempt was made by Sprengling and Freeman[8] to determine which methylol derivatives form when phenol is treated with a small excess of formaldehyde (ratio 1:1.4). The method employed was methylation of the reaction mixture followed by oxidation. Results

were as follows:



The first practical method for the separation of mixtures of polymethylolphenols was developed by Martin.[9] The phenol alcohols were separated as their trimethylsilyl derivatives by fractional distillation, the derivatives being obtained by treatment of the phenol-aldehyde reaction products with trimethylchlorosilane in the presence of pyridine.

$$ROH + (CH_3)_3\,Si\,Cl \xrightarrow{\text{Pyridine}} RO\text{-}Si(CH_3)_3 + [HCl]$$

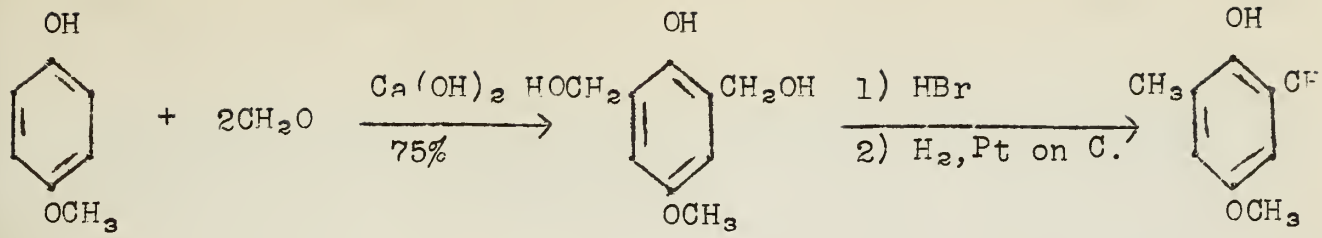
The trimethylsilyl derivatives are then hydrolyzed to the phenol alcohols. Martin lists the following properties of the trimethylsilyl derivatives which makes them especially well suited to the separation at hand. They are easily prepared, are thermally stable, resistant to air oxidation and are easily hydrolyzed under neutral conditions. This last is especially important as a number of the polymethylolphenols are very sensitive to acids and bases.

By this method Martin was able to prepare and separate p-methylolphenol, 2,4-dimethylolphenol and 2,4,6-trimethylolphenol from the reaction of two moles of formaldehyde and one of phenol.

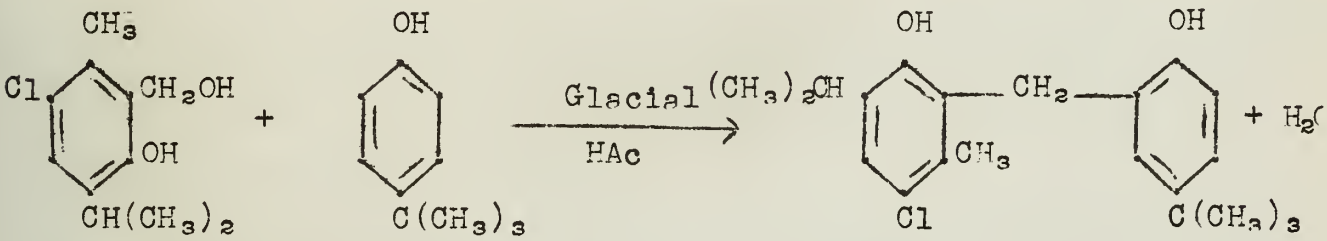
Perhaps the best procedure presently available for the preparation of methylolphenols is given by Ruderman.[10] He emphasizes that experimental conditions are often very critical due to the fact that the reaction may proceed beyond the desired hydroxyl stage to produce condensed products such as dihydroxydiphenylmethane and higher polymers. It is also pointed out that when an oil is obtained upon acidification of the reaction mixture, the best procedure is to subject the oil to intense refrigeration to induce crystallization <u>in situ</u> rather than to extract the oil with ether and attempt to crystallize the ether extract.

The synthesis of some polymethylolphenols by other means has been completed recently.[11,12] The method used was the reduction of the corresponding esters with lithium aluminum hydride. It was by this process that 2,4,6-trimethylolphenol was first synthesized by Carpenter and Hunter.[11]

A number of ring-methylated phenols have been synthesized by converting methylolphenols to the corresponding halomethylphenols, followed by hydrogenolysis of the halomethyl groups.[13]



Unsymmetrical diarylmethanes may be prepared by condensation of a Lederer-Manasse methylol product with some other phenol.[14]



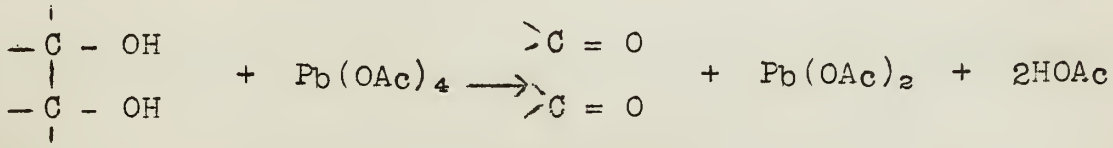
BIBLIOGRAPHY

1. Greene, Compt. Rend., 90, 40; Am. Chem. J., 2, 19 (1880).
2. A. Baeyer, Ber., 5, 25 (1872); 5, 280 (1872).
3. O. Manasse, ibid., 27, 2409 (1894).
4. L. Lederer, J. prakt. Chem., 50, 223 (1894).
5. K. Auwers and Anselmino, Ber., 35, 137 (1902); Auwers and van de Rovaart, Ann., 302, 105 (1898); Auwers and Erklentz, ibid., 302, 115 (1898); Manasse, Ber., 35, 3844 (1902); Bamberger, ibid., 36, 2036 (1903).
6. K. Auwers, ibid., 40, 2524 (1907).
7. F. S. Granger, Ind. Eng. Chem., 24, 442 (1932).
8. G. R. Sorengling and J. H. Freeman, J. Am. Chem. Soc., 72, 1982 (1950).
9. R. W. Martin, ibid., 74, 3024 (1952).
10. Ruderman, ibid., 70, 1662 (1948).
11. Carpenter and Hunter, Plastics, 287 (1950); J. Applied Chem., 1, 217 (1951).
12. J. H. Freeman, J. Am. Chem. Soc., 74, 6257 (1952).
13. W. J. Moran, E. C. Schreiber, E. Engel, D. C. Behn, and J. L. Yamins, ibid., 74, 127 (1952).
14. H. E. Faith, ibid., 72, 837 (1950).

A NEW MECHANISM FOR THE OXIDATION OF GLYCOLS BY LEAD TETRAACETATE

Reported by Joanne G. Arnheim May 15, 1953

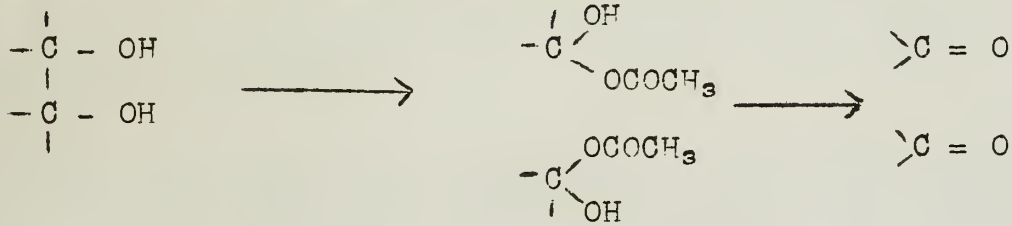
In 1931 Criegee[1], working with cyclopentadiene oxidation by lead tetraacetate, found that an impurity, cyclopentanediol, was reacting in the following manner:



He found the reaction to be general for all glycols which possess at least two hydroxyl groups on two neighboring carbon atoms. The products obtained were aldehydes and ketones, according to the glycol used, by a fission between the two hydroxyl groups.[2]

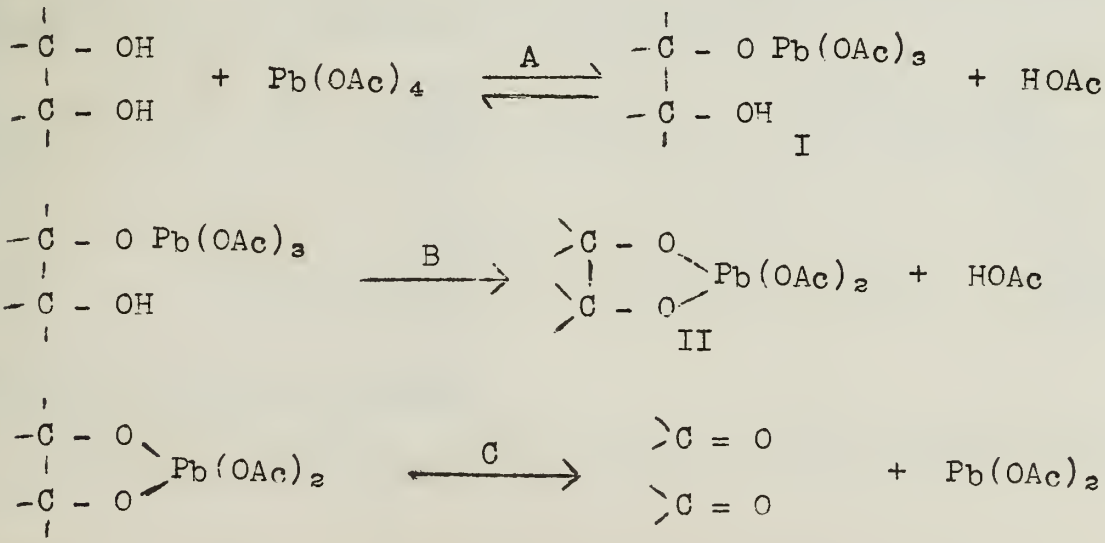
Mechanism Proposed by Criegee

Criegee became interested in this reaction and in 1931 proposed that the reaction followed this scheme:



which involves an initial attack on the carbon atom attached to the hydroxyl group. This mechanism doesn't explain the fact, however, that only glycols and not their ethers or esters undergo this cleavage.

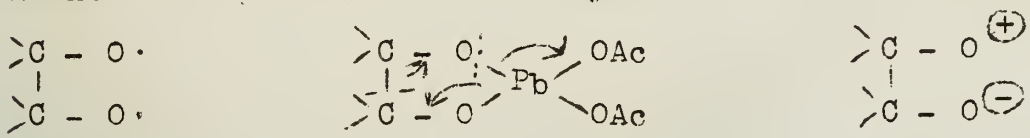
Therefore, after further study on the chemistry and kinetics of the reaction, he proposed the following mechanism.[3]



Criegee has shown that HOAc retards the rate of the reaction, whereas non-polar solvents like benzene and nitrobenzene accelerate the reaction. Traces of hydroxylic solvents present in the HOAc are

found to accelerate the reaction also.[4] This fact supports the evidence for stage A- an equilibrium - before the rate determining step. Kinetic evidence pointed to a second order reaction, corresponding to B as the slow stage. He has also proven the existence of compounds like I since $Pb(OAc)_2(OH)(OCH_3)$ was obtained as the product of the reaction of $Pb(OAc)_4$ with methyl alcohol.

In the decomposition of II the quadrivalent lead becomes divalent. Criegee has said it may occur in one of three ways.[1]

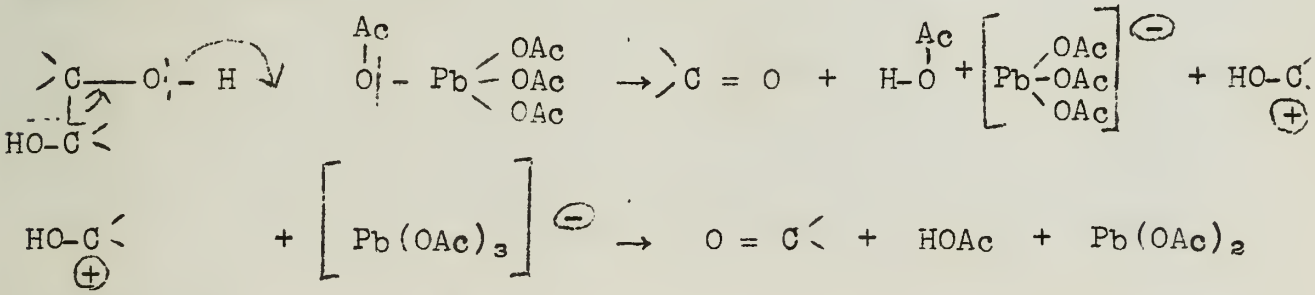


III IV V

Such radicals as III are known to be unstable and break between th two carbon atoms thus leading to the expected products. IV is mor likely, as it is similar to the intermediate in the periodic acid type of oxidation, involving the shift of six electrons. V is jus as likely as III and would group glycol cleavage with numerous othe reactions in which a cationic oxygen atom affords the driving forc for a cleavage of a C-C bond.

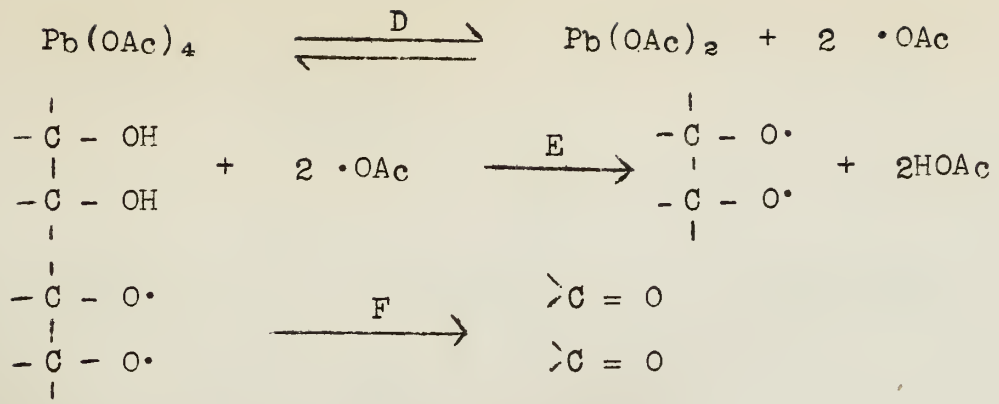
As further evidence for the existence of the cyclic intermediate, Criegee has shown that cis-glycols, especially those of five membered rings, which have rigid cis valences, react much mor rapidly than the corresponding trans compounds.[1,5] For example, the rate constant, k_2, for cis-cyclopentanediol at 20° is greater than 40,000 while the corresponding constant for the trans compound is 12.8.

A surprise behavior of trans-9,10-decalin was noted by Criegee.[5] Ring formation is, for spatial reasons, entirely excluded, yet the diol reacts smoothly and not especially slowly with $Pb(OAc)_4$. To explain this, he has recently proposed a different reaction mechanism in this case.[1]



<u>Mechanism Proposed by Waters</u>

Waters,[6,7] however, seemed to prefer a free radical reaction. He proposed the following:



reaction (D) being the slow step. His reasons for such a mechanism are that Fieser and Kharasch have shown (D) to occur and that the acetoxyl radical should be stabilized by resonance.

Bell, Sturrock, and Whitehead[8] studied the kinetics of the fission of ethylene glycol and showed it to be first order with respect to both the glycol and the $Pb(OAc)_4$. By determining the A in the Arrhenius equation, $k=Ae^{-E/RT}$, theoretically and experimentally, they concluded that the steric factor was approximately unity. This seemed to be evidence for a radical rather than an ionic mechanism.

Evidence Against A Free Radical Mechanism

Kharasch,[9,10] in an attempt to prove whether $Pb(OAc)_4$ decomposed in the following manner:

1. $Pb(OAc)_4 \longrightarrow Pb(OAc)_2 + 2CH_3COO\cdot \longrightarrow 2CH_3\cdot + CO_2$

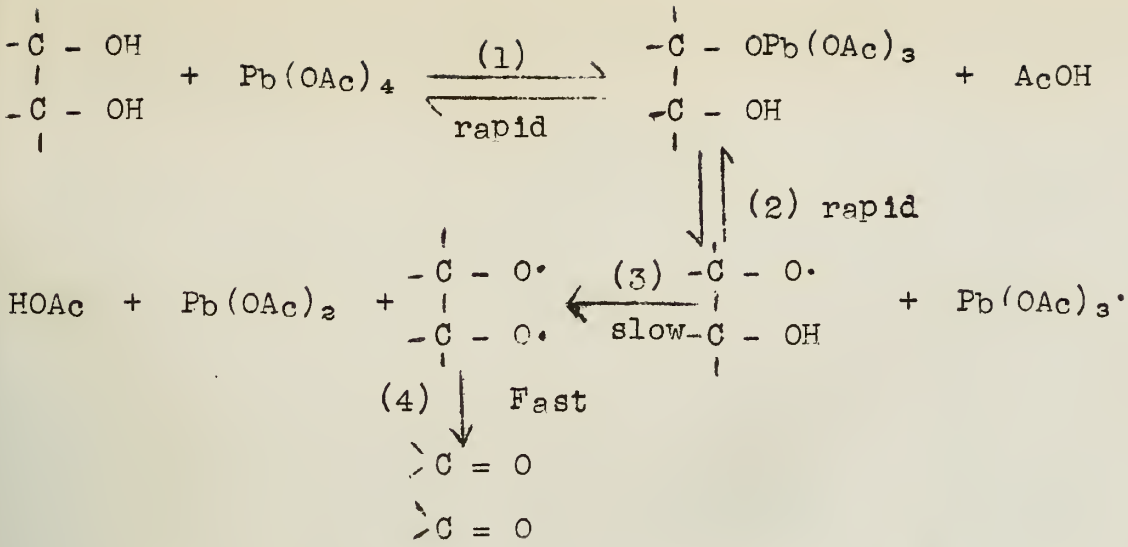
   or

2. $Pb(OAc)_4 \longrightarrow Pb(OAc)_2 + (CH_3COO)_2$

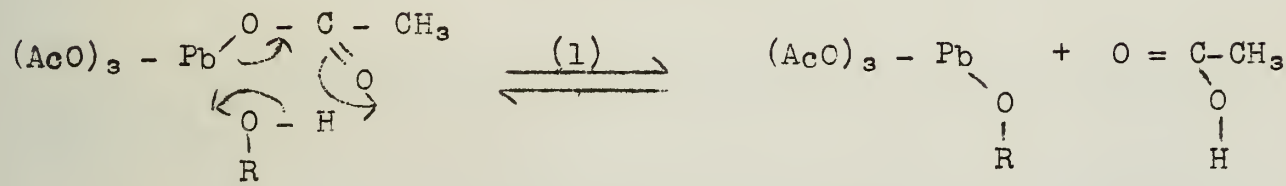
compared the products of the reaction of butanediol and of hydrobenzoin with diacetyl peroxide and with $Pb(OAc)_4$. In the case of the diacetyl peroxide, the products consisted mainly of hydroxy aldehydes and diketones instead of the normal glycol fission products. He noted, too, that the reaction of $Pb(OAc)_4$ and diacetyl peroxide with acetic acid lead to different products, to acetoacetic acid and to succinic acid respectively. He concluded, therefore, that the reactions of $Pb(OAc)_4$ do not proceed by an initial decomposition into lead diacetate and acetoxyl radicals.

New Mechanism

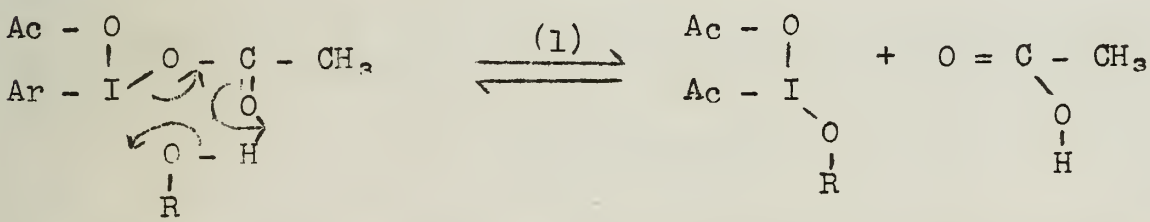
Recently Cordner and Pausacker,[11] after redetermining the order of the reaction and the constants in the Arrhenius equation for ethylene glycol, propylene glycol, glycerol α-monochlorohydrin, isobutyl tartrate, pinacol, pinacol hydrate, and a number of substituted benzopinacols, at various temperatures, proposed the following mechanism:



The following scheme was proposed for stage (1):



The above scheme is supported by the fact that of the substituted benzopinacols used, electron releasing groups (CH_3, OCH_3) accelerated the reaction, whereas electron attracting groups (Cl) retarded it. Thus, when the electron availability on the oxygen atom was increased, the equilibrium was shifted further to the right. Work on the aryl iodosoacetates,[12] which are capable of the same action as $Pb(OAc)_4$, has supported this theory.



When electron attracting groups were present in the aryl group, the equilibrium was shown to be farther to the right by an increase in the rate constant.

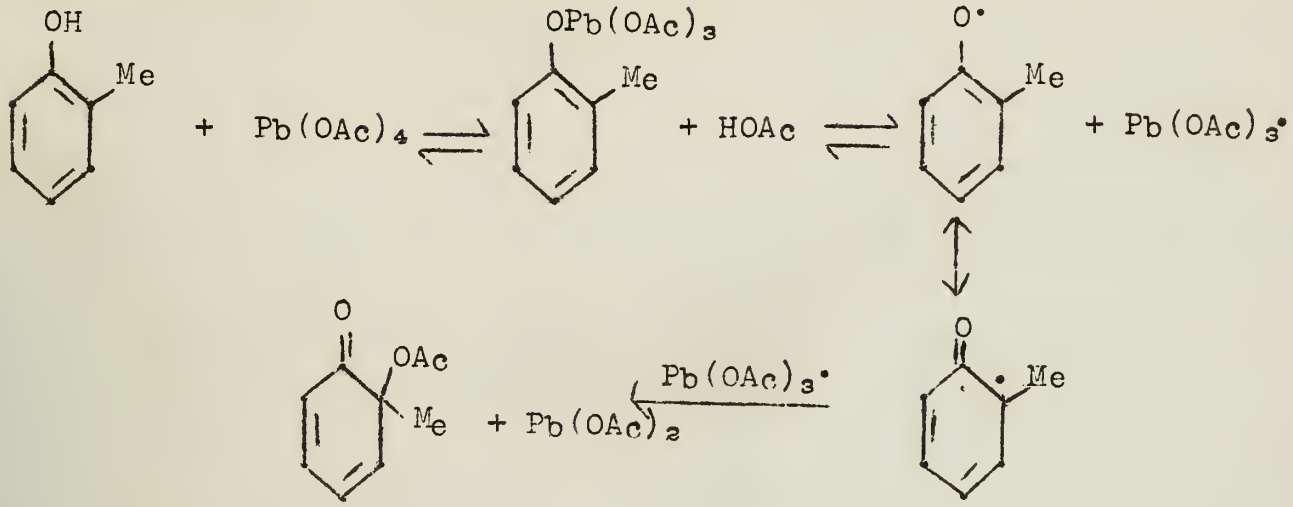
Stage 2 represents a normal dissociation of quadrivalent lead compounds, postulated by Kharasch and co-workers.[10]

The products resulting from stage 3 and their subsequent decomposition are the same as those that have already been postulated by Waters for this reaction. This homolytic fission is preferred for several reasons over Criegee's cyclic intermediate:

1. It would make this radical action of $Pb(OAc)_4$ consistent with nearly all of the other reactions of this compound.

2. The oxidation of phenols by $Pb(OAc)_4$ can be explained by this type of mechanism. Phenols are oxidized to derivatives of

cyclohexadienone, that is, o-cresols yield 2-acetoxy-2-methylhexa-3 5-diene-1-one.



3. The oxidation of trans-9,10-decalin does not have to be accomodated by a different mechanism from that of the oxidation of other glycols.

4. Even the crucial fact that cis-glycols are oxidized more readily than the trans compounds can be explained. It is known that glycols with free rotation (that is, cis-glycols) display intramolecular hydrogen bonding, whereas trans-glycols would be bonded intermolecularly. Thus, whereas only one of the hydrogen atoms of the glycol will participate in hydrogen bonding in cis-glycols, both hydrogen atoms may participate in trans-glycols thus decreasing the rate of the reaction.

Therefore, it may be seen that all of the facts can be as satisfactorily explained by this mechanism as by Criegee's.

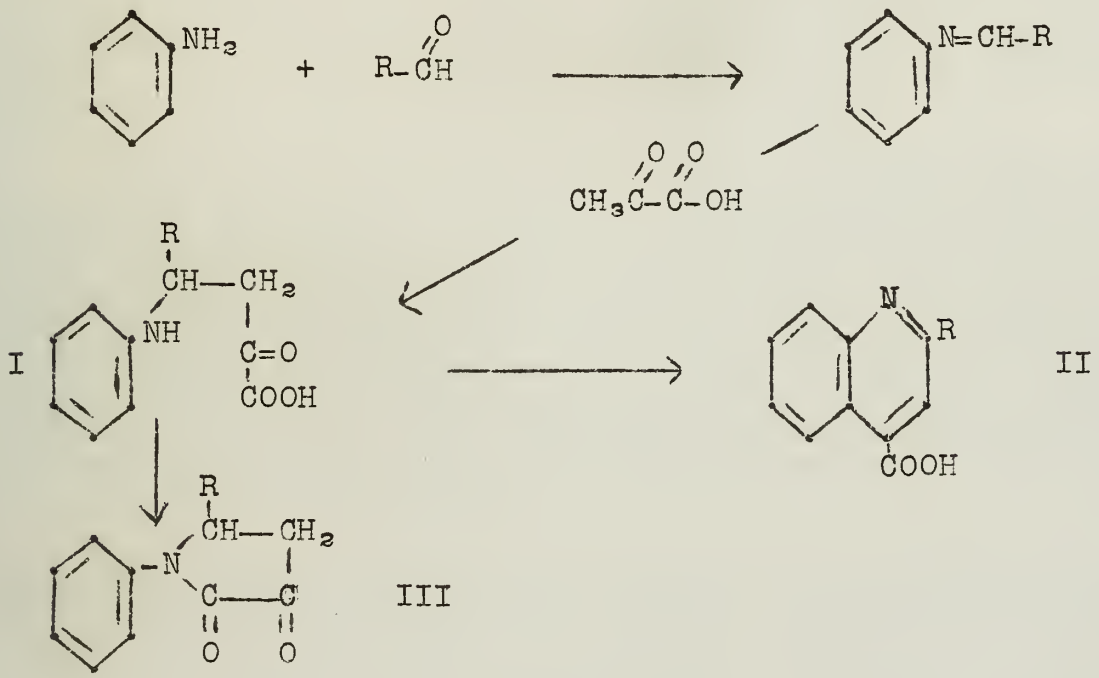
BIBLIOGRAPHY

1. Criegee, R., Organic Chemistry Seminars, Massachusetts Institute of Technology, September 26, 1951.
2. Criegee, R., Ber. 64, 1931, 260.
3. Criegee, R., Kraft L., and Rank O., Ann., 507, 1933, 159.
4. Criegee, R. and Büchner, Ber., 73, 1940, 563.
5. Criegee, R., Buchner, E., and Walther, W., Ber., 73, 1940, 571.
6. Waters, J., J. Chem. Soc., 1939, 1805.
7. Waters, J., "Chemistry of the Free Radicals" Oxford, 1949, 228.
8. Bell, R. P., Sturrock, J. G. R., and Whitehead, R. L., J. Chem. Soc., 1940, 82.
9. Kharasch, M. S., Friedlander, H. N. and Urry, W. H., J. Org. Chem., 14, 949, 91.
10. Kharasch, M. S., Friedlander, H. N., and Urry, W. H., J. Org. Chem., 16, 1951, 533.
11. Cordner, J. P. and Pausacker, K. H., J. Chem. Soc., 1953, 102.
12. Pausacker, K. H., J. Chem. Soc., 1953, 107.

2,3-Pyrrolidinediones

Reported by Clayton T. Elston May 15, 1953

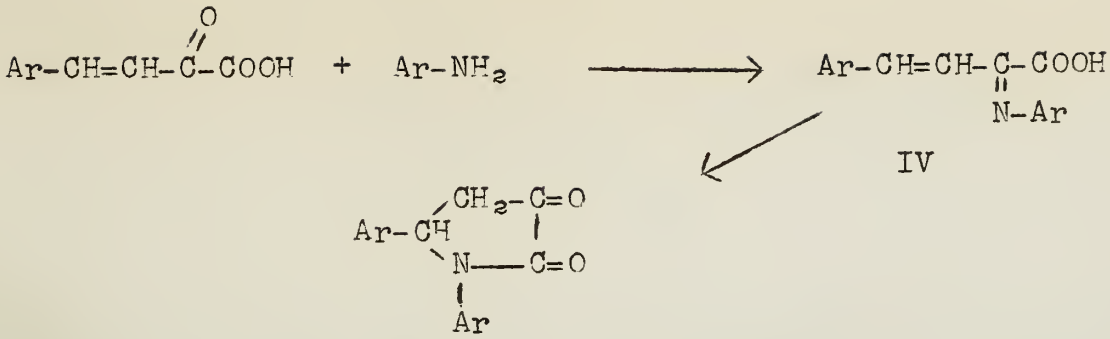
In 1887 Doebner[1] discovered that cinchonic acids could be synthesized by the condensation of an aromatic amine with a pyruvi acid and an aldehyde. He noticed also that a neutral product was often formed in the reaction mixture. The neutral product predominated if the reaction was carried out at room temperature while higher temperatures (100°) favored the formation of the cinchonic acid. Schiff and Bertini[2] postulated the 2,3 pyrrolidinedione structure for these compounds and the following reaction scheme was later proposed by Borsche[3]. α-Ketobutyric acids, of



the type I, are known to be formed in such reaction mixtures but their reluctance to undergo ring closure casts some doubt upon their role as intermediates.[4,5] The pyrrolidinedione structure III has been verified by independent synthesis.[6]

Infrared absorption spectra of such compounds show a hydroxyl band at 2.93μ, indicating that they exist at least partially in the enolic form.

Bodforss[7] found that when benzylidenepyruvic acid was treated with aniline it yielded the anil, α-phenylimino-β-benzylidenepropionic acid IV, which on heating in acetic acid produced the

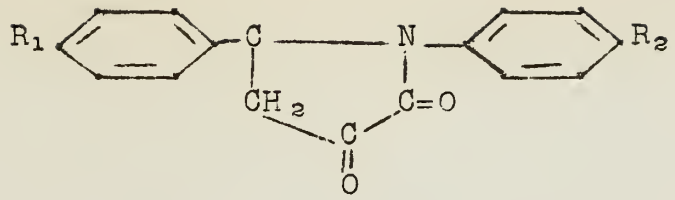


corresponding pyrrolidinediones. However, only pyrrolidinediones were produced in this reaction. Work recently reported by Vaughan and Peters gives some evidence that α-iminopropionic acids are als intermediates in the synthesis involving the anil and the pyruvic acid.[6] Thus, the cinchonic acid synthesis and the pyrrolidinedion synthesis may involve different intermediates.

Johnson and Adams[8] were the first to observe the unusual decarboxylation reaction of 1,5-diaryl-2,3-pyrrolidinediones. They found that the product obtained by the condensation of arsanilic acid, benzaldehyde and pyruvic acid evolved carbon dioxide when heated to its melting point. Although such a reaction was consistent with the cinchonic acid structure other reactions of the compound, such as the occurrence of aniline in the sodium hydroxide fusion products indicated the pyrrolidine structure. Recently Vaughan and Peters[6] have identified the decarboxylation products of such compounds as anils of cinnamaldehydes and have also studie the decarboxylation reaction.

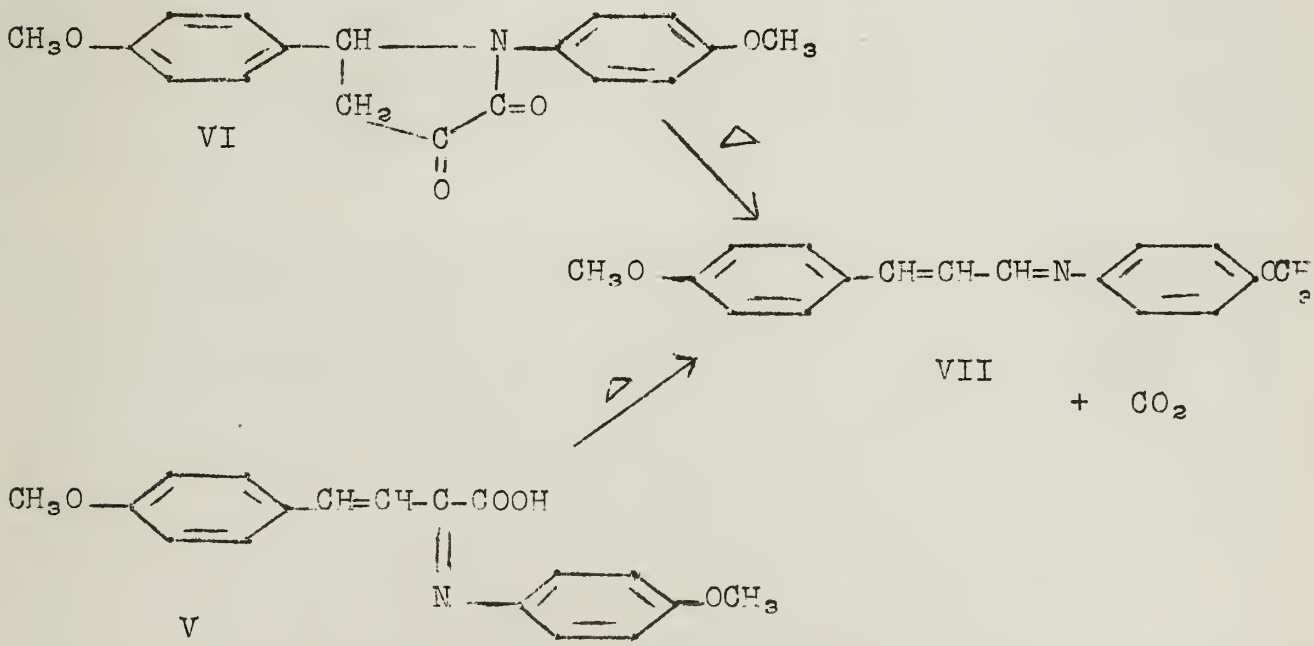
The thermal decomposition of the type exhibited by 1,5-diaryl-2,3-pyrrolidinediones is not a general reaction of N-substituted α-ketoamides. Benzylidenepyruvanilide (ArCH=CH-CO-CO-NH-Ar) was found to be stable under the conditions which led to carbon dioxid evolution in the pyrrolidine compounds. Pyruvanilide shows a similar stability. The reaction appears to depend also on the position of the substituents in the pyrrolidine ring. Thus, 1,4-diphenyl-2,3-pyrrolidinedione and 1,4,5-triphenyl-2,3-pyrrolidinedione are stable under the reaction conditions. It may be noted that distillation of the latter compound yielded stilbene as well as unidentified products.[3]

Vaughan and Peters[9] prepared eight 1,5-diaryl-2,3-pyrrolidinediones and determined the rate constants of the decomposition reaction at various temperatures. Dilute solutions of the pyrrolidinedione (0.2 - 0.4%) in o-dichlorobenzene were used in the rate studies, and in all cases the reaction was found to follow first order kinetics. In comparing the rate constants for the substituted pyrrolidinediones they found that an electron-releasing substituent (CH_3O-) in position R_1 or R_2 increased the rate of decomposition while an electron-withdrawing group ($-NO_2$) had the reverse effect. In general, the effect of a substituent at R_2 on the rate is less than the effect of the same substituent at R_1.



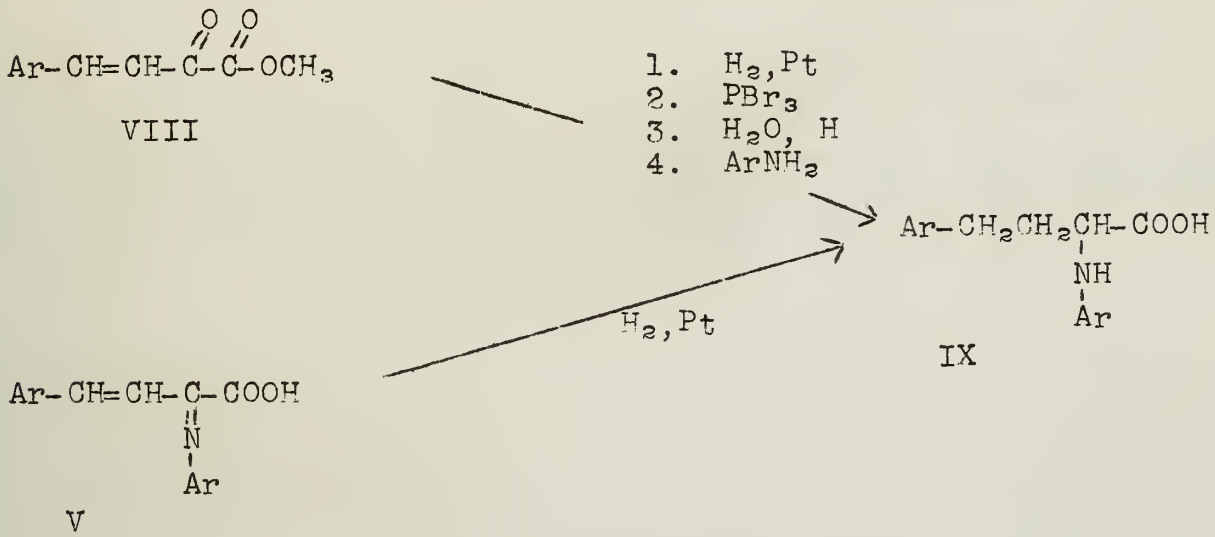
The rate constants were found to be dependent on the solvent employed in the reaction. Quinoline showed a marked accelerating effect on the decomposition of 1,5-diphenyl-2,3-pyrrolidinedione. The first order rate constant varies almost linearly with the amount of quinoline added to the o-dichlorobenzene solution of the pyrrolidine. The initial concentration of the pyrrolidinedione was also found to affect the rate constants to some extent. This might be expected in view of the acceleration observed with quinoline and since the product of the decomposition is basic.

The authors propose that the thermal decomposition of the 1,5-diaryl-2,3-pyrrolidinedione proceeds through the isomeric α-arylimino-β-benzylidenepropionic acids.[10] Evidence that such an equilibrium does indeed exist is supported by numerous lines of evidence. β-Anisylidene-α-anisyliminopropionic acid V and 1,5-dianisyl-2,3-pyrrolidinedione VI undergo decomposition with elimination of carbon dioxide to yield N-(4-methoxycinnamylidene)-4'-anisidine VII. These compounds were selected for study because the former could be prepared and purified without extensive rearrangement to the isomeric 2,3-pyrrolidinedione. A plot of log K vs 1/T (where K= the first order rate constant, T= the absolute temperature) for the decomposition reaction of the two compounds shows complete congruence. Compounds of type V can be converted



to VI by recrystallization from a large volume of acetic acid-ethanol. This conversion proceeds so rapidly that purification of the α-iminopropionic acids by crystallization is not usually possible.

The reverse transformation can be effected by warming VI with a small volue of methanol. However, 1,5-diansyl-2,3-pyrrolidinedione was the only pyrrolidinedione which could be isomerized to the α-iminoacid upon warming with alcohol. The structure of the α-iminoacid V was determined by reduction to α-anisylamino-γ-anisylbutyric acid IX with hydrogen over platinum. Compound IX was also synthesized from benzylidene methyl pyruvate VIII.



A freshly prepared methanolic solution of either V or VI exhibits a changing ultraviolet absorption spectrum. The two spectra become identical after several hours. Both solutions show absorption maxima at 324 mμ and 230 mμ. The intensity of the 324 mμ band decreases with time for solutions of V while the same band shows increased intensity with time for solutions of VI. After standing several weeks the solutions show a new absorption band at 269 mμ which is different from the decarboxylation product and that of methyl anisylidenepyruvate. The nature of the secondary reaction is not known. At room temperature solutions of VI in di-n-butyl ether show a constant spectrum but at elevated temperatures the spectrum changes in a manner which indicates that decarboxylation is occurring.

A suspension of V in methanol-dioxane can be titrated with sodium hydroxide to give a normal titration curve. Similar curves were obtained for the titration of VI. The electrical conductivity of freshly prepared methanol solutions of VI increases on standing and gradually reaches an equilibrium value. By assuming that the conductance of the non-ionic species VI is negligible and that the molar conductance of V is equal to the molar conductance of the similar α-anisylamino-γ-anisylbutyric acid the equilibrium constant for the reaction VI $\rightleftarrows$ V was found to be 0.298 at 25°. The average rate constant for the conversion of VI → V in methanol at 25° was calculated to be 1.4×10^{-3} min^{-1}. The rate constant for the decomposition of VI in o-dichlorobenzene at 100° was shown to be 1.18×10^{-2} min^{-1}. Assuming a doubling of rate for each 10° rise in temperature, the conversion of VI → V would be eighteen times as fast as decarboxylation at the same temperature.

$$VI \overset{fast}{\rightleftarrows} V \xrightarrow{slow} CO_2$$

BIBLIOGRAPHY

1. O. Doebner, Ann., 242, 265 (1887).
2. R. Schiff and C. Bertini, Ber., 30, 601 (1897).
3. W. Borsche, ibid., 42, 4072 (1909).
4. H. T. Bucherer and R. Russischwili, J. prakt. Chem., 128, 59 (1930).
5. F. Misani and M. T. Bogert, J. Org. Chem., 10, 458 (1945).
6. W. R. Vaughan and L. R. Peters, ibid., 18, 382 (1953).
7. S. Bodforss, Ann., 455, 41 (1927).
8. J. R. Johnson and R. Adams, J. Am. Chem. Soc., 45, 1307 (1923).
9. W. R. Vaughan and L. R. Peters, J. Org. Chem., 18, 393 (1953).
10. W. R. Vaughan and L. R. Peters, ibid., 18, 405 (1953).

PRODUCTS OF o-PHENYLENEDIAMINES AND ALLOXAN IN NEUTRAL SOLUTION

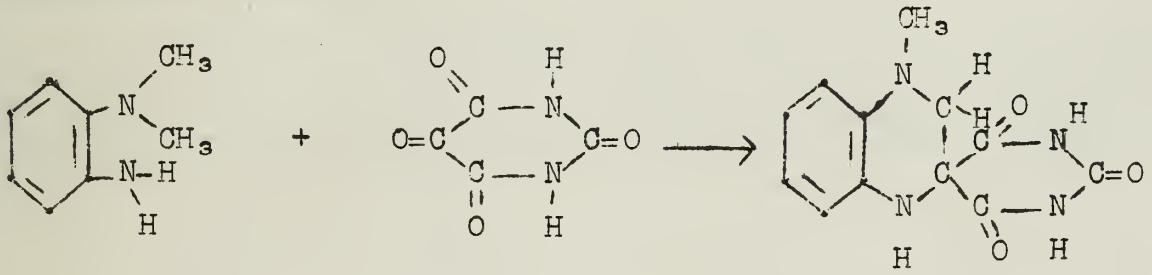
Reported by Harold H. Hughart May 15, 1953

It is well known that the hydrochlorides of diprimary and primary-secondary o-phenylenediamines react with alloxan, forming alloxazines and isoalloxazines. The condensation of alloxan with free o-phenylenediamines, however, follows a different course, and forms products which have generally been formulated as alloxan anils. The acceptance of this type of structure hinges largely on the work[1] of Rudy and Cramer, who allowed alloxan to react with o-dimethylamino-aniline. The product is typical, and seemingly required the anil structure.

But these compounds fail to undergo the expected acid hydrolysis, nor are they cyclized in acid media to alloxazines or isoalloxazines. Further, their visible and u.v. absorption spectra differ markedly from that of the previously described[2] 5-p-dimethylamino anil. King and Clark-Lewis, accordingly, undertook the reinvestigation[3,4,5] of these compounds.

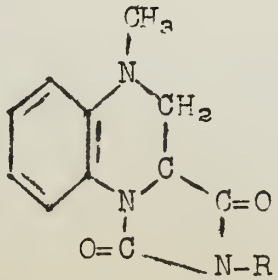
Primary, Tertiary o-Diamines[3]

The product of the reaction of alloxan with o-dimethylamino-aniline was shown by a Herzig-Meyer determination to contain only one N-methyl group. The other methyl group, as well as the primary amino nitrogen must have reacted with the alloxan, and probably at the 5 position, to give a six-membered ring of the hydroquinoxaline system, I.

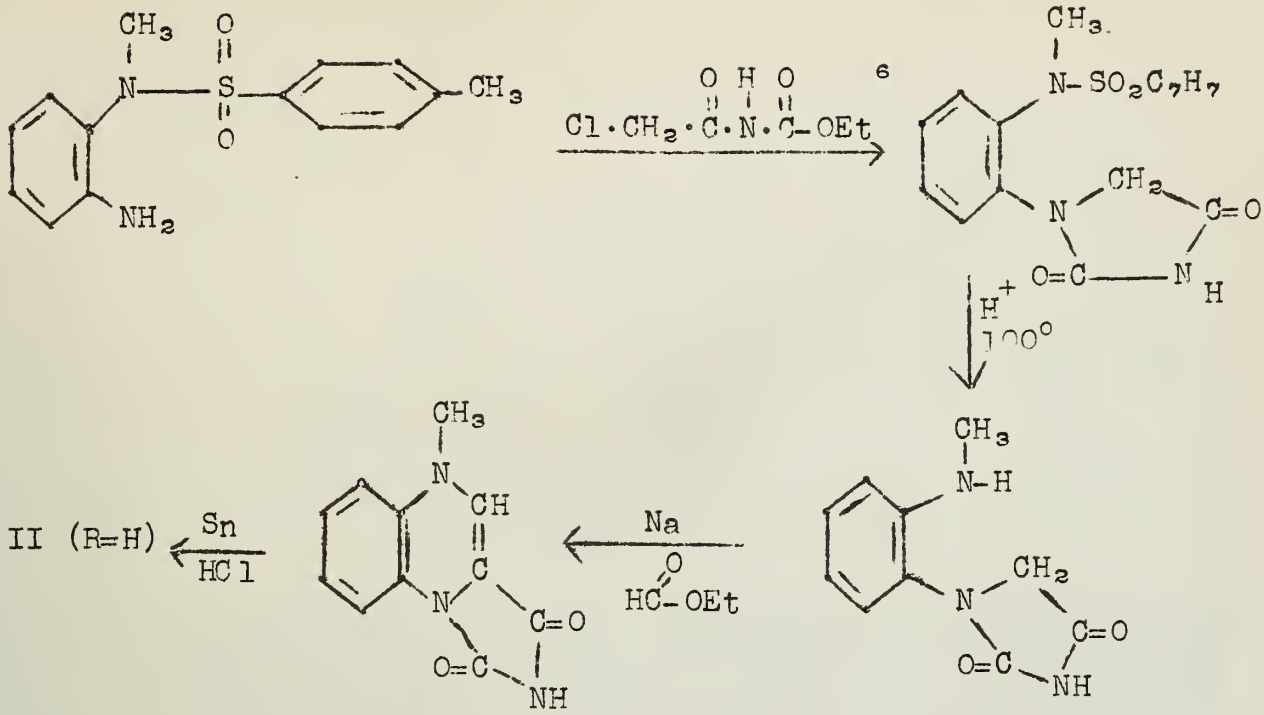


I

Methylation of this product with diazomethane replaced two hydrogens and left a compound with one replaceable hydrogen (Zerewitinoff method), thus corresponding to the above formula. By 30% aqueous sodium hydroxide, I is transformed into a compound having a similar u.v. absorption spectra but one $\overset{O}{\overset{\|}{C}}-\overset{H}{N}$ fragment less. That this has the structure II (R=H) has been shown by synthesis.



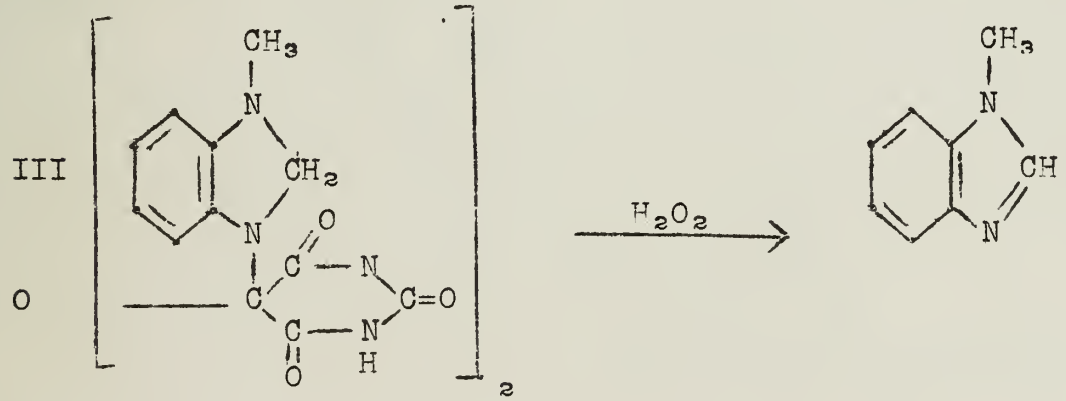
II



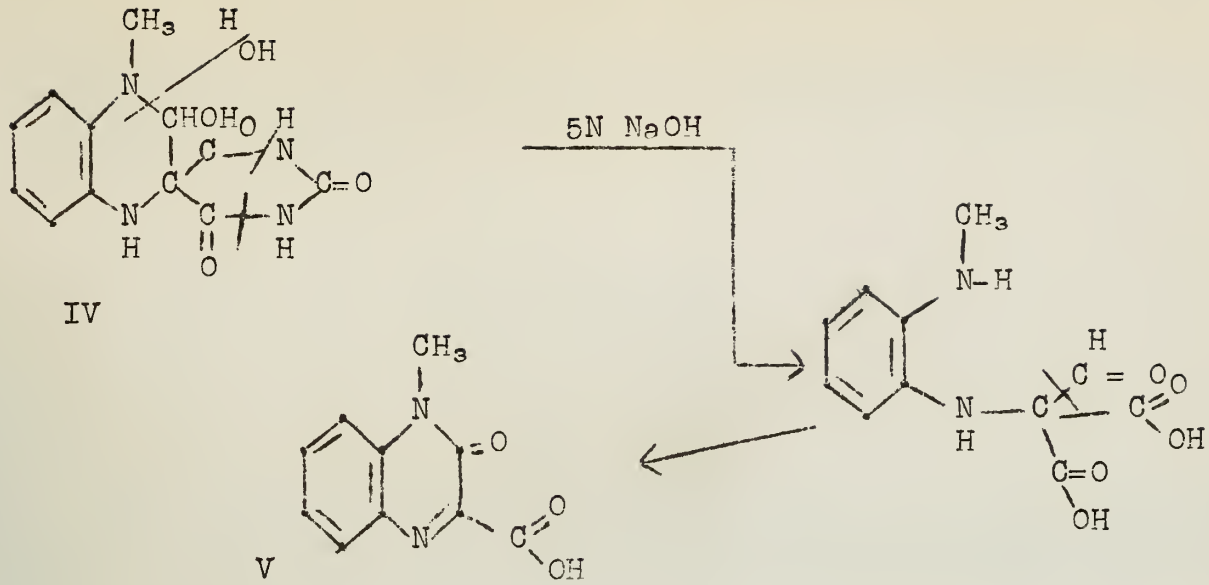
This type of alkaline degradation (I → II) has been observed[7] previously. The structure of II thus, serves to fix the structure of I, especially since the u.v. absorption spectra support the preservation of the hydroquinoxaline system.

By-Product Formation[5]

Accompanying the spiran in the condensation of alloxan with o-dimethylamino aniline is an ether. This was considered by Rudy and Cramer to contain the benzimidazole structure III, since vigorous oxidation with hydrogen peroxide converts it into 1-methyl benzimidazole.



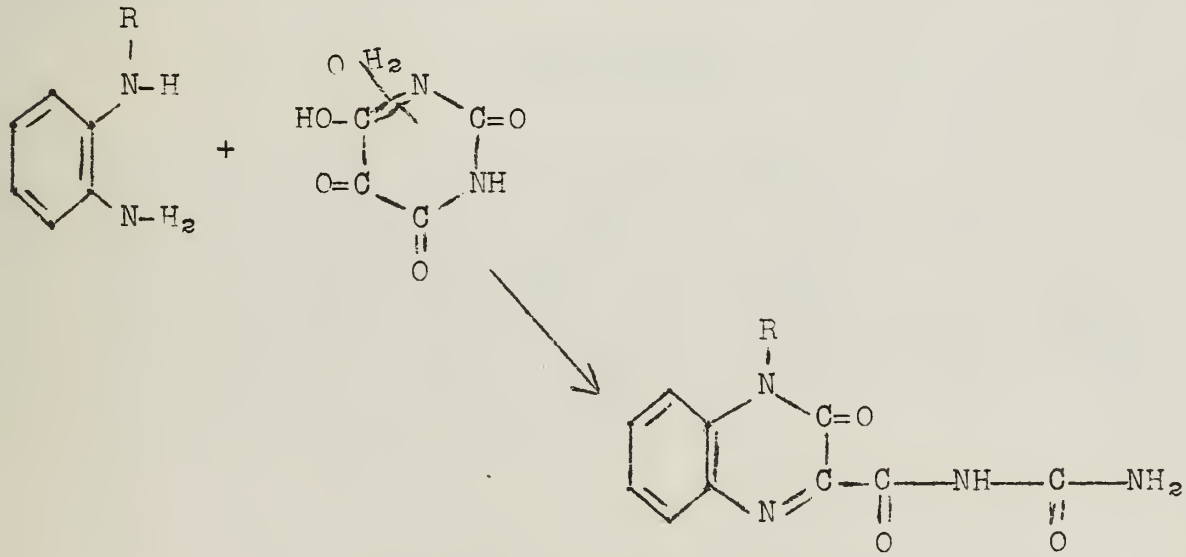
However, since the ether can be obtained merely by the action of molecular oxygen or alloxan on the spiran, I, the two are presumably structurally similar. On this basis, King and Clark-Lewis have formulated the ether as an anhydride of the alcohol IV (R=H); this alcohol can be obtained by boiling the ether with water, or by oxidation of the spiran I with molecular oxygen in boiling water. This latter synthesis is comparable with the preparation of pseudo strychnine from strychnine.[8] IV (R=H) reacts on alkaline hydrolysis to produce V and formic acid, substantiating structure



Compound IV is resistant to acid hydrolysis; this behavior would not be expected in a structure with a carboxyureide chain in place of the barbiturate ring. However, IV does not form ethers with simple alcohols. This has been attributed to its low solubility in these reagents.

Primary and Secondary o-Diamines[4]

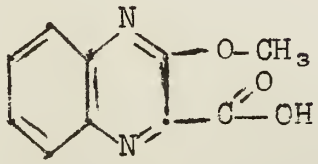
Diprimary and primary-secondary o-phenylenediamines react with alloxan to form products showing the characteristic quinoxaline u.v. absorption maxima and minima.[9] These have been demonstrated to have the structure VI.



VI (R=H, alkyl, aryl)

If VI (R=H) is methylated by diazomethane, the product is the O-methyl ether, as shown by a Zeisel determination. This can be

hydrolyzed by cold, aqueous sodium hydroxide to 3-methoxy-quinoxaline-2-carboxylic acid, VII, identified by comparison with a synthetic specimen.



VII

The constitution of the product VI($R=CH_3$) was also determined by acid hydrolysis to the corresponding quinoxaline-2-carboxylic acid. An identical acid can be synthesized from N-methyl-o-phenylenediamine and ethyl mesoxalate.

Compounds V (R=H, $R=CH_3$) react with methyl iodide-potassium carbonate to form the same trimethyl derivative. Diazomethane treatment of VI (R=H) replaces only one hydrogen, giving VI, ($R=CH_3$).

o-Amino-diphenylamine condenses with alloxan to form a typical quinoxaline, VI (R=phenyl). It is less stable than the N-alkyl derivatives, however, and slowly deposits o-amino-diphenylamine from cold 1 N alkali.

The 2-alkylamino-3-aminopyridines form two series of products with alloxan. One is yellow and unstable, readily changing to the second, colourless, stable form. The structures are not known.

BIBLIOGRAPHY

1. Rudy and Cramer, Ber., 71, 1234 (1938).
2. Piloty and Finckh, Ann., 333, 37 (1904).
3. King and Clark-Lewis, J. Chem. Soc., 3080 (1951).
4. King and Clark-Lewis, ibid., 3379 (1951).
5. King and Clark-Lewis, ibid., 172 (1953).
6. Frerichs and Breustedt, J. Prakt. Chem., 66, 231 (1902).
7. King and Clark-Lewis, J. Chem. Soc., 3077 (1951).
8. Leuchs, Ber., 70, 1543 (1937).
9. Kuhn and Bär, Ber., 67, 898 (1934).

RECENT SYNTHESES OF THIAZOLES AND THIAZOLINES FROM AMINONITRILES

Reported by N. E. Bojars May 22, 1953

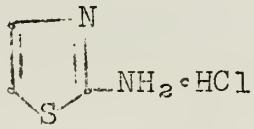
HISTORICAL. Thiazole (I) and thiazoline (II) compounds can be readily obtained by various methods, which have been worked out largely by Hantzsch.

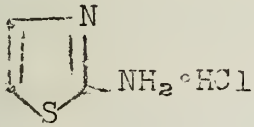
(I)

(II)

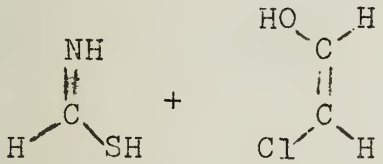
Several preparative methods are known for the compounds (I) and (II). A useful synthesis of (I) and some of its derivatives has been worked out by Traumann,[1] Naf,[2] and Popp;[3] thiourea serves as a reagent.

(1) $ClCH_2\text{-}CHClOC_2H_5 + H_2O \rightarrow HCl + C_2H_5OH + [ClCH_2CHO]$

(2) $[ClCH_2CHO] + (NH_2)_2CS \rightarrow H_2O +$ 

(3)  + $ONCC_2H_5$ $\xrightarrow[\text{ethanol}]{\text{in}}$ 

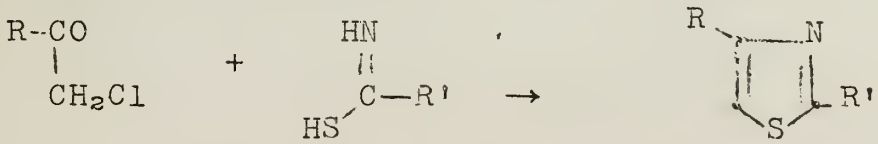
Another synthesis of (I) employs thioformamide and chloroacetaldehyde hydrate.[4]

(4)  $H_2O \rightarrow$  $+ 2H_2O + HCl$

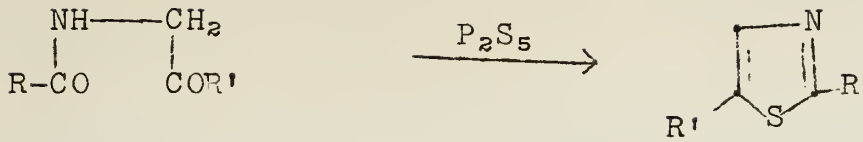
Thioformamide is also useful in the preparation of thiazoline.[4]

(5)   $+ NH_4Br$

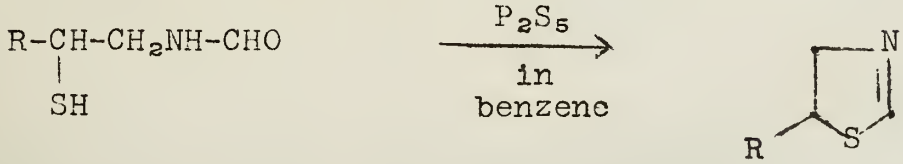
The general reaction (6) has been developed by Hantzsch.[5]

(6) 

Of several other methods the one originated by Gabriel[6,7] can be mentioned. Acylated aminoaldehydes, aminoketones, and amino-acid esters react with phosphorus (V) sulfide to produce thiazoles.[6]

(7) 

Formamidoalkylmercaptans yield thiazolines.[7]

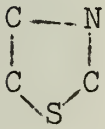
(8) 

Thiazole and thiazoline themselves also can be made by this general method involving the use of phosphorus (V) sulfide.[6,7]

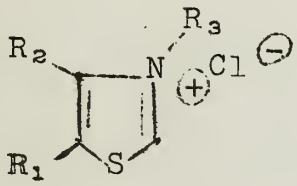
<u>The Properties of Thiazoles and Thiazolines</u>. Thiazoles are quite stable compounds.[5] They show little tendency to react with nitric acid, and are not affected by the usual reducing agents. They form stable salts with acids,[5] which have an acid reaction, while the aqueous solutions of free thiazoles are neutral. The odor of thiazoles is similar to that of pyridine compounds,[7] and the two types show similarities of the chemical behavior and of the physical constants.

Thiazolines and thiazoles behave similarly; however, the former are stronger bases.

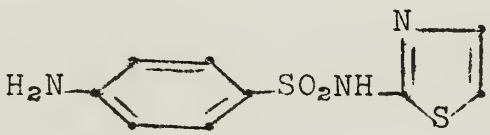
The ring structure (III) can be found in the nuclei of penicillins. Thiazolinium salts, of which vitamin B_1 is an example, have the general formula (IV).



(III)



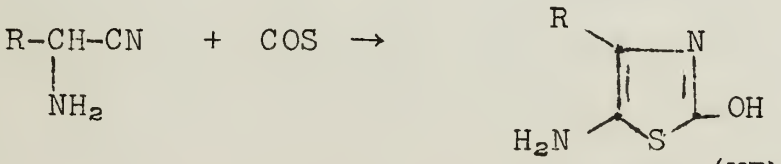
(IV)



(V)

Sulfathiazole (V) is among the most useful of the sulfa drugs.

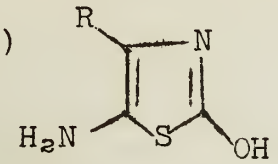
<u>The Reaction of Aminonitriles with Carbon Oxysulfide</u>. A. H. Cook, Sir I. Heilbron and coworkers have published recently a series of articles "Studies in the azole series." A part of this series[8] discloses a new method of synthesis of thiazoles from α-aminonitriles and carbon oxysulfide.

(9) 

(VI)

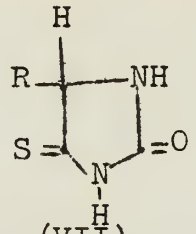
The structure proof of the compounds (VI) (R = C_6H_5 or CO_2Et) was carried out by several reactions,[8] among others, by the preparation of a benzylidene derivative with benzaldehyde, which confirmed the

existence of the amino group in (VI). The authors[8] also investigated the rearrangement of 5-amino-2-hydroxythiazoles (VI) into thiohydantoins (VII).

(10) 

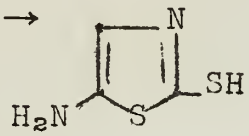
(VI)

Raney Ni
→
or aqueous alkali

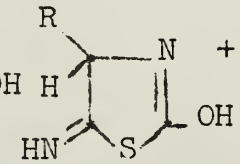


(VII)

Aminoacetonitrile reacts with carbon oxysulfide to produce intractable tars; however, the former can be used in the synthesis of 2-mercapto-5-aminothiazole.[8]

(11) $H_2NCH_2CN + CS_2 \rightarrow$ 

While 2-phenyl-2-aminoacetonitrile and 2-carbethoxy-2-aminoacetonitrile react according to the equation (9), it is remarkable that 2-alkyl-2-aminoacetonitriles yield instead iminothiazolines.[9]

(12) $R\text{-}CH(NH_2\cdot HCl)\text{-}CN + COS + CH_3ONa \xrightarrow[CH_3OH]{in}$  $+ NaCl + CH_3OH$

(VIII)

The compounds of the general formula (VIII), where R is a methyl, ethyl, n-propyl, or n-hexyl group, are yellow crystals, insoluble in most organic solvents except the amines like pyridine and methylmorpholine.[9] They are soluble in dilute alkali and ammonia, and are reprecipitated by acidification. A sodium salt has been isolated in one case. The imine structure (VIII), in contrast to the amine structure (VI), is proved by the absence of amine reactions; these alkyl derivatives do not react with benzaldehyde, for instance. On the contrary, they show typical imine reactions.[9]

BIBLIOGRAPHY

1. V. Traumann, Ann. 249, 36 (1888).
2. E. Näf, Ann. 265, 110 (1891).
3. G. Popp, Ann. 250, 275 (1889).
4. R. Willstatter and T. Wirth, Ber. 42, 1908 (1909).
5. A. Hatzsch, Ann. 250, 257 (1889).
6. S. Gabriel and M. Bachstez, Ber. 47, 3170 (1914).
7. S. Gabriel, Ber. 49, 1112 (1916).
8. A. H. Cook, Sir I. Heilbron, and G. D. Hunter, J. Chem. Soc. 1949, 1443.
9. J. Parrod and L. Van Huyen, Compt. rend. 236, 933 (1953).

THE MECHANISM OF THE SANDMEYER REACTION

Reported by A. B. Galun May 22, 1953

In 1884 Sandmeyer[1] tried to obtain phenylacetylene from benzene diazonium chloride and copper (I) acetylide, but found that he obtained chlorbenzene. Later he used copper (I) salts instead of acetylides[2] discovering thereby a method for introducing halogens into aromatic nucleii, which proved to be a very useful synthetic tool.

The first kinetic studies of this reaction were carried out by Waentig and Thomas[3] in 1913. They reported that the reaction was first order in diazonium ion, was accelerated by an increase in total copper (I) chloride and retarded by hydrogen chloride. They also isolated complexes of the type $X \cdot C_6H_4 \cdot N_2ClCu_2Cl_2$.

Some ten years ago a radical mechanism was proposed by Waters and an ionic mechanism by Hodgson (an interesting pictorial presentation was given earlier by Hantzsch and Blagden[4].)

Water's radical mechanism[5] can be represented as follows:

$$1.\quad Cu.^{+} + Ar\text{-}\overset{+}{N}{=}N \longrightarrow Cu^{++} + Ar\cdot + :N{\equiv}N:$$

$$2.\quad Ar\cdot + Cl^{-} \longrightarrow Ar\text{-}Cl + e$$

$$3.\quad e + Cu^{++} \longrightarrow Cu^{+}\cdot$$

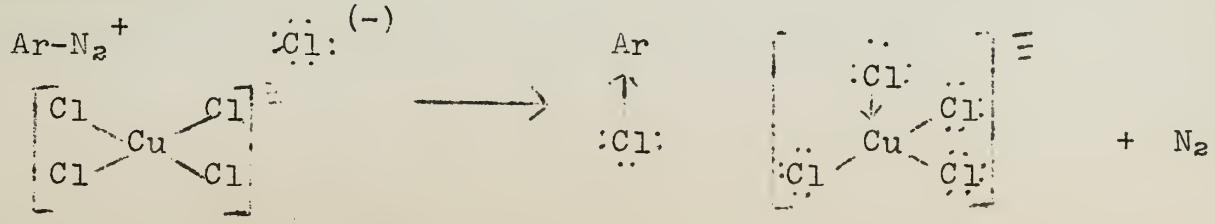
Waters postulated that the essential role of the copper (I) ion in the Sandmeyer reaction is its ability to participate in steps involving transfer of a single electron, and that in the gattermann modification (metallic copper catalyst) an electron is first donated by metallic copper. The formation of the side products, Ar-Ar and Ar-N=N-Ar, is easily accounted for: $2Ar\cdot \longrightarrow Ar\text{-}Ar$

and $Ar\cdot + Ar\text{-}\overset{+}{N}{=}N \longrightarrow [Ar\text{-}\dot{N}{=}\ddot{N}\text{-}Ar]^{+}$;

$$[Ar\text{-}\dot{N}{=}\ddot{N}\text{-}Ar]^{+} + e \longrightarrow Ar\text{-}N{=}N\text{-}Ar$$

The main objections to this mechanism are[6]: 1) the absence of extensive reactions between Ar· and water to yield phenols and hydrocarbon 2) the entire absence of unsymmetrical diaryls of the type ArC_6H_4Cl 3) the fact that an increase in diazonium ion concentration does not increase the yield of azo compound 4) the mechanism necessitates the assumption that during nitrile synthesis the radical always reacts preferentially with the copper (I) cyanide even in solutions containing an excess of chloride ions.

Hodgson's ionic mechanism[7-11] is essentially a nucleophilic displacement:



The complex $[CuCl_4]^{=}$ is regarded as a halogen carrier. In order to prove that the oxidation of copper (I) ions is not the important stage (as Waters claimed), he showed that several metallic salts in their highest state of oxidation, such as $CuCl_2$ or $SnCl_4$ can also catalyze the reaction[9]. The formation of biphenyl and azo compounds is explained by Hodgson as involving the radical mechanism proposed by Waters.

A kinetic study by Cowdry and Davies[6] proved that the reaction is first order with respect to both diazonium ion and dissolved copper (I) chloride; the rate is, however, inversely proportional to the square of the total chloride ion concentration. They inferred that the primary reaction is a collision between ArN_2^+ and $CuCl_2^-$ ions. At higher chloride ion concentration $CuCl_2^-$ is converted into unreactive $[CuCl_4]^{=}$, so that $CuCl_2^- + 2Cl^- \rightarrow [CuCl_4]^{=}$ is acutally the retarding reaction. The following mechanism was suggested:

a) a slow coordination of the terminal nitrogen atom of ArN_2^+ to the copper in $CuCl_2^-$ giving $[ArN_2CuCl_2]$ b) decomposition of this complex to ArCl or c) further fast addition to it of ArN_2^+ to give $[(ArN_2)_2CuCl_2]^+$, which then either d) decomposes to ArCl or e) reacts with $CuCl_2^-$ to give ArN=NAr.

This mechanism is consistent with the effect of electron withdrawing groups such as NO_2 which increase the rate of the reaction.

Hodgson's displacement mechanism does not explain the fact that increased chloride ion concentration retards the reaction, and it necessitates a completely separate formulation of the side reactions.

Recently Pfeil and Velten[12,13] pointed out that the ion $[CuCl_4]^{=}$ does not exist in detectable amounts under the conditions of the Sandmeyer reaction. Since $[CuCl_3]^{=2}$ exists in solution in appreciable concentrations and since the rate of the reaction is inversely proportional to the square of the chloride ions they assume that copper (I) chloride itself is the catalyst. They further assume that while the Sandmeyer reaction is first order with respect to copper (I) chloride, the two side reactions

$$2(ArN_2^+) + 2CuCl \longrightarrow ArN{=}NAr + N_2 + 2(CuCl)^+ \quad \text{and}$$

$$2(ArN_2^+) + 2CuCl \longrightarrow Ar{-}Ar + 2N_2 + 2(CuCl)^+$$

are second order with respect to copper (I) chloride. Hence, the observation that the side products become predominant if the concentration of copper (I) ions is increased, is explicable. By increasing the chloride ion concentration the formation of a copper complex is favored, thereby decreasing the copper (I) ion concentration and suppressing the side reactions.

The authors postulate the following mechanism:

1. $[CuCl_3]^{=} \rightleftharpoons CuCl + 2Cl^-$ (this step controls the concentration of the catalyst and therefore the rate and yield)
2. $(R\text{-}N_2)^+ + CuCl \longrightarrow [R\text{-}N{=}N\ CuCl]^+$
3. $[R\text{-}N{=}N\ CuCl]^+ \longrightarrow [R\cdot + Cu^{II}Cl^+] + N_2$
4. $[R\cdot + Cu^{II}Cl^+] \longrightarrow RCl + Cu^+$
5. $Cu^+ + 3Cl^- \longrightarrow [CuCl_3]^{=}$

The by-products are formed by following bimolecular reactions (which consume catalyst):

$$2[R\text{-}N_2{:}\ Cu^{(I)}Cl] \longrightarrow R\text{-}N{=}N\text{-}R + N_2 + 2Cu^{II}Cl^+$$

$$2[R\text{-}N_2{:}\ Cu^{I}Cl] \longrightarrow R\text{-}R + 2N_2 + 2Cu^{II}Cl^+$$

The authors showed that copper (II) ions cannot act as catalyst, and were reduced in Hodgsons' experiments by free amine (present through a reversal of the diazotation)[14] On the other hand, copper (II) ions form a complex with copper (I) ions[16] thereby suppressing the side reaction and increasing the yield, though retarding the reaction rate. Increase of chloride ion concentration increases also the yield, but may retard the reaction to such an extent that heating becomes necessary. Leonards obtained in some cases a 100% yield by working according to these considerations.

BIBLIOGRAPHY

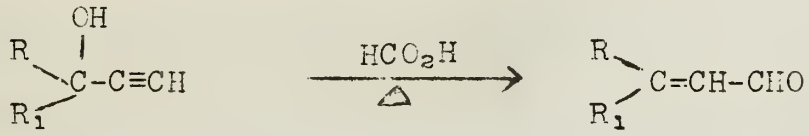
1. T. Sandmeyer, Ber., 17, 1633, 2650 (1884).
2. T. Sandmeyer, Ber., 23, 1880 (1890).
3. P. Waentig and J. Thomas, Ber., 46, 3923 (1913).
4. A. Hantzsch and J. W. Blagden, Ber., 33, 2545 (1900).
5. W. A. Waters, J. Chem. Soc., 1942, 268.
6. W. A. Cowdrey and D. S. Davies, J. Chem. Soc. Suppl., 1949, 48-59.
7. H. H. Hodgson, S. Birtwell and J. Walker, J. Chem. Soc., 1941, 770.
8. H. H. Hodgson, S. Birtwell and J. Walker, J. Chem. Soc., 1942, 376, 720.
9. H. H. Hodgson, S. Birtwell and J. Walker, J. Chem. Soc., 1944, 18.
10. H. H. Hodgson and Sibbald, J. Chem. Soc., 1944, 393.
11. H. H. Hodgson and Sibbald, J. Chem. Soc., 1945, 819.
12. E. Pfeil and O. Velten, Ann. Chem. Justus Liebigs, 562, 163 (1949).
13. E. Pfeil and O. Velten, Ann. Chem. Justus Liebigs, 565, 183 (1949).
14. E. Pfeil and O. Velten, Angew. Chem., 65, 155 (1953).
15. Leonards, Dissertation Marburg (Germany) (1952).
16. Kohlschütter, Ber., 37, 1170 (1904).

THE ALLEGED RUPE REARRANGEMENT

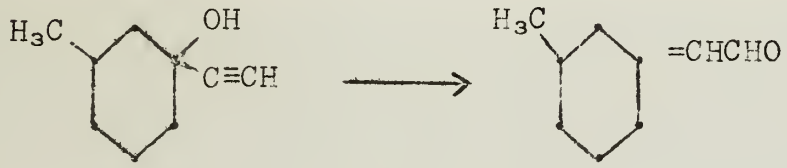
Reported by William P. Samuels May 22, 1953

The product resulting from the Meyer-Schuster rearrangement of acetylenic carbinols containing a free ethynyl would be expected to be an α,β-unsaturated aldehyde, and since these compounds are not very easily accessible it appeared that this type of rearrangement would offer a convenient method of synthesis.

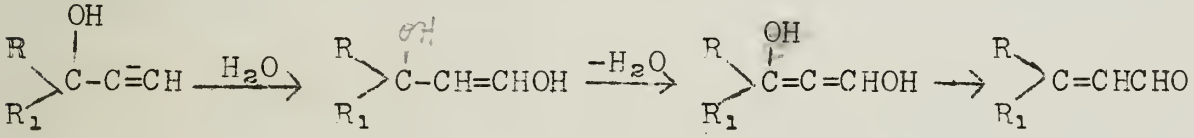
In 1926 Rupe and Kambli[1] reported the rearrangement of acetylenic carbinols in the presence of 80% formic acid to unsaturated aldehydes according to the equation:



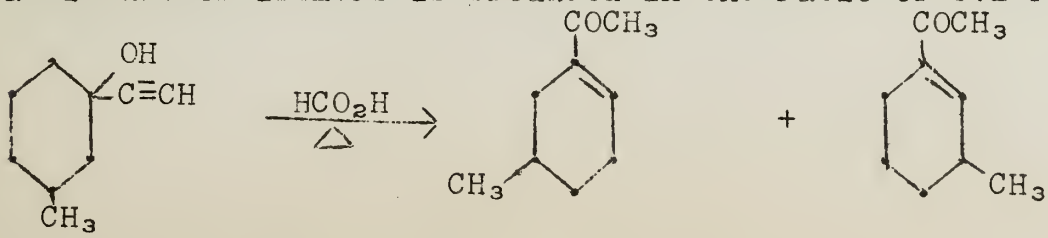
The product obtained from 3-methyl 1-ethynyl 1-cyclohexanol by this method was reported to be 3-methyl-cyclohexylidene acetaldehyde in 80% yield.



Rupe[2] proposed a mechanism analagous to that of Meyer and Schuster involving the addition of water and then subsequent loss of water followed by rearrangement to the unsaturated aldehyde:



The method was then extended to include the rearrangement of a considerable number of tertiary acetylenic carbinols. Some yielded aldehydes and some ketones. The aldehyde forming carbinols included the acetylenic carbinols synthesized from fenchone[3], tetrahydrocarvone[3], cyclohexanone[2], methyl isohexyl ketone[4], β-phenylethyl methyl ketone[5,6], acetone[1], ethyl methyl ketone[1], acetophenone[4], and the acetylenic carbinol resulting from a mixture of d-isomenthone and l-menthone[7]. The products were all reported as α,β-unsaturated aldehydes. The acetylenic carbinols synthesized from 4-methylcyclohexanone[8], β-phenylethyl methyl ketone[5,6], and 3-methylcyclohexanone[9] were reported to yield α-β-unsaturated ketones. With the last mentioned compound a mixture of isomers is produced in the ratio of 3:1 respectively:

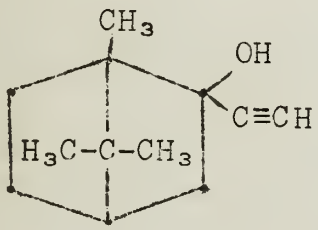


In attempting to rearrange the acetylenic carbinol of methylheptenone with formic acid Rupe and Lang[10] obtained a tetrahydropyran derivative:

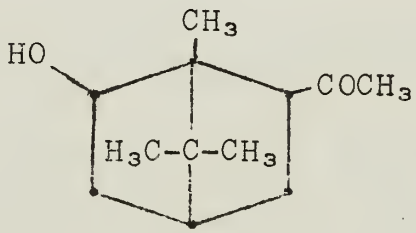
Kilby and Kipping[11] have reported a similar rearrangement with the acetylenic carbinol of dimethylheptenone.

The validity of Rupe's results were first questioned by Fischer and Lowenberg[12] as a result of their projected synthesis of phytol. They reinvestigated Rupe's work and found that the products were invariably unsaturated ketones. Other workers who were unable to obtain aldehydes were Davies, Heilbron, Jones, and Lowe[13], and Dimroth[14].

In view of this Hurd and Christ[15] reexamined the reaction in some detail. They found that the product obtained from 1-ethynylcyclohexanol was 1-acetylcyclohexane. Ethynyl phenyl methyl carbinol gave a small amount of acetophenone, and not β-phenylcrotonaldehyde as reported by Rupe and Giesler[4]. The main product obtained here was a tar probably resulting from the polymerization of $CH_2 = C(C_6H_5) - C(=O) - CH_3$. The acetylenic carbinol of camphor, ethynylbornyl alcohol (I) yielded 2-acetyl-6-hydroxycamphane (II). The conversion of (I) to (II) involves two Wagner rearrangements.



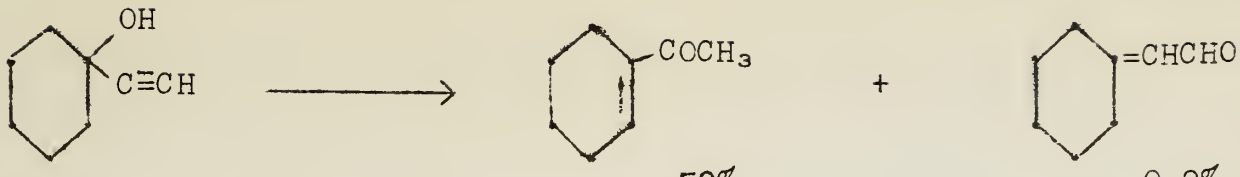
I

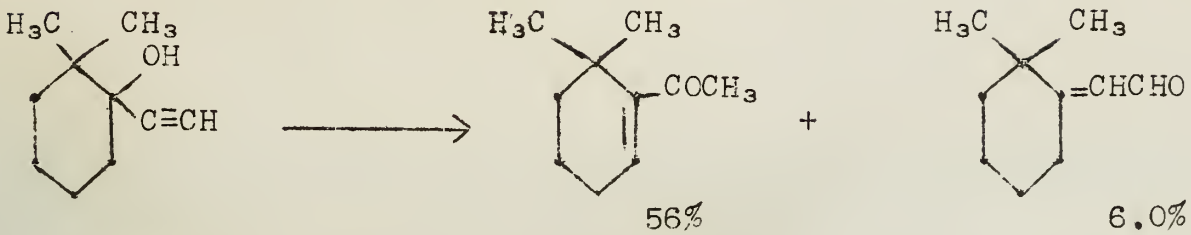


II

Hurd and McPhee[16] found that dimethyl ethynyl carbinol gave $CH_2 = C(CH_3)-C \equiv CH$ resulting from dehydration along with a small amount of $CH_2 = C(CH_3)-COCH_3$. Rupe and Kamble[1] reported dimethylacrolein as the product.

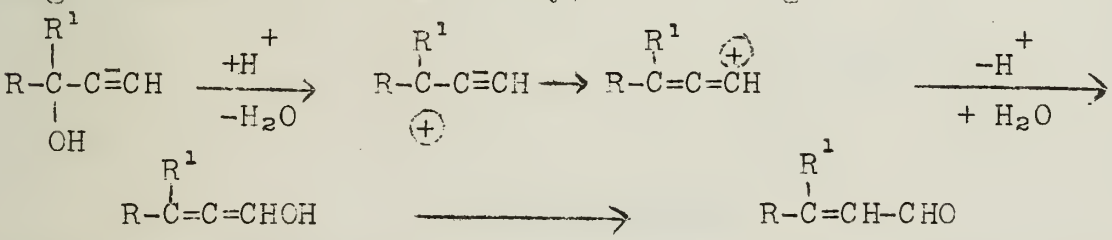
Chanley[17] has found aldehydes as minor products in the compounds he investigated. This is in agreement with the faint aldehyde tests obtained by Rupe and Hurd.





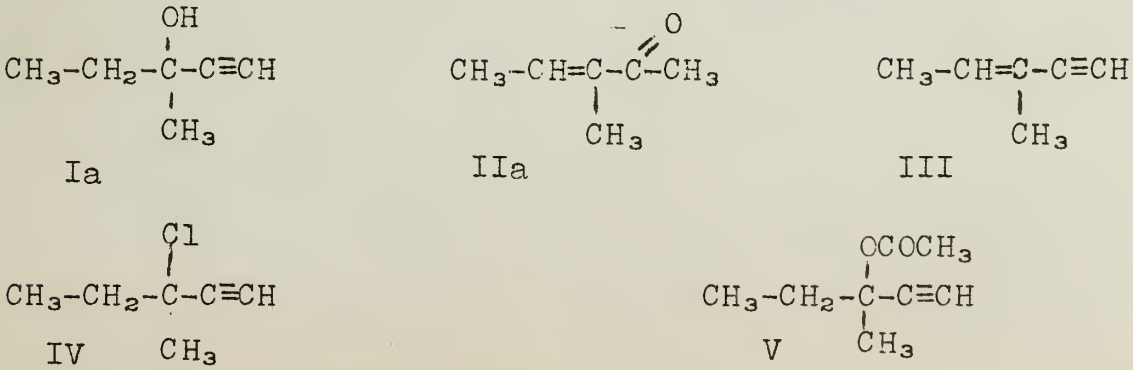
Recently Hennion et al.[18] studied the action of formic acid on dialkyl ethynylcarbinols and found the reaction to be best represented by:

and not unsaturated aldehydes as proposed by Rupe. Aldehydes would be expected if the reaction followed the course of the Meyer-Schuster rearrangement which involves an anionotropic migration similar to the allylic rearrangement:

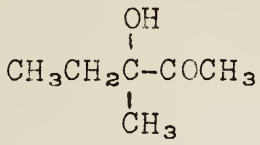


The Rupe reaction is thus an apparent 1,2 shift of the hydroxyl while the Meyer-Schuster is a 1-3 or allylic shift.

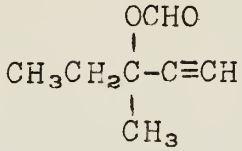
In studying (Ia) Hennion found the product to be (IIa) and not "S-butylidene acetaldehyde" as reported by Rupe[1]. They proved that (IIa) was formed by the dehydration of the carbinol (Ia) to 3-methyl 3-penten-1-yne (III) and subsequent hydration of the triple bond. This conclusion emerged from the observation that the carbinol (Ia), the corresponding vinyl acetylene (III), the chloride (IV), and the acetate ester (V) yielded the same product (IIa) upon treatment with hot formic acid.



That hydration of the triple bond did not precede the dehydration was evident from the fact that the acyloin (VI) did not react with hot formic acid.



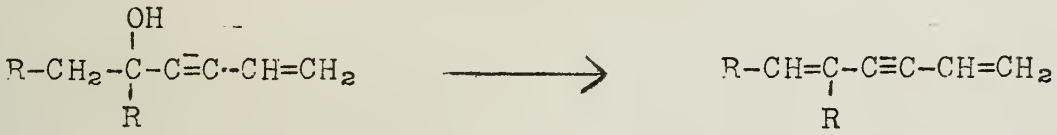
VI



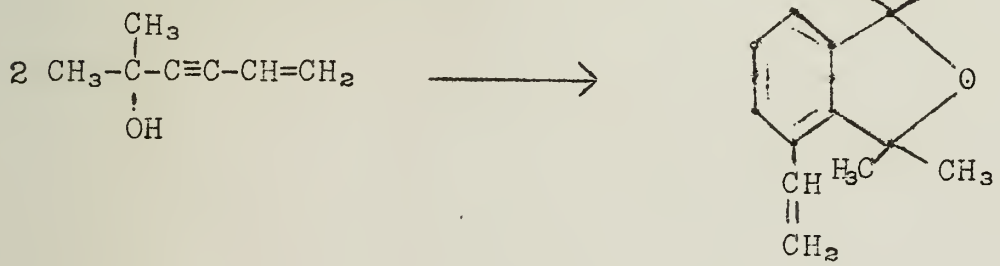
VII

The alternate explanation involving thermal decomposition of the formate ester (VII) was considered untenable since (VII) was not decomposed by heating above its boiling point.

Russian workers[19,20,21] attempted to extend the rearrangement to vinylethynyl carbinols but found that treatment with formic acid according to Rupe or acetic acid and sulfuric acid according to Meyer and Schuster led to dehydration:



In one case they obtained a dimer:



BIBLIOGRAPHY

1. Rupe and Kambli, Helv. chim. Acta., 9, 672 (1926).
2. Rupe, Messner, and Kambli, ibid., 11, 449 (1928).
3. Rupe and Kuenzy, ibid., 14, 708 (1931).
4. Rupe and Giesler, ibid., 11, 656 (1928).
5. Rupe and Herschmann, ibid., 14, 687 (1931).
6. Rupe and Werdenberg, ibid., 18, 542 (1935).
7. Rupe and Gassmann, ibid., 17, 283 (1934).
8. Rupe and Kuenzy, ibid., 14, 701 (1931).
9. Rupe, Haecher, Kamble, and Wassieleff, ibid., 16, 685 (1933).
10. Rupe and Lang, ibid., 12, 1133 (1929).
11. Kilby and Kipping, J. C. S., 1939, 435.
12. Fischer and Löwenberg, Ann., 475, 183 (1929).
13. Davies, Heilbron, Jones, and Lowe, J. C. S., 1935, 586.
14. Dimroth, Ber., 71, 1933 (1938).
15. Hurd and Christ, J. A. C. S., 59, 118 (1937).
16. Hurd and McPhee, ibid., 71, 399 (1949).
17. Chanley, ibid., 70, 244 (1948).
18. Hennion, Davis, and Maloney, J. A. C. S., 71, 2813 (1949).
19. Nazarov, Nagibina, and Zaretskayce, Bull. acad. sci., U. R. S. S., Classe sci. chim., 1940, 447; C. A. 35, 5092 (1941).
20. Nazarov and Elizarova, ibid., 1940, 223; ibid., 36, 746 (1942).
21. Nazarov and Verkholetova, ibid., 1941, 556; ibid., 37, 2343 (1943).